VISIT…



EQUINE NEUROLOGY

Edited by Martin Furr and Stephen Reed



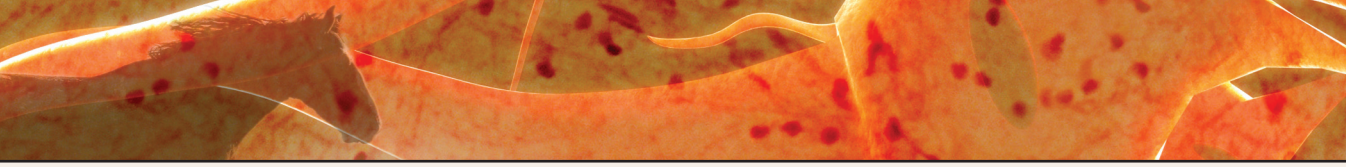
Blackwell Publishing

EQUINE NEUROLOGY

Edited by Martin Furr and Stephen Reed



Blackwell Publishing



EQUINE NEUROLOGY

Edited by Martin Furr and Stephen Reed

Interest in and recognition of equine neurologic disease have advanced in recent years to the point that it is a common part of clinical practice. In this practical and comprehensive clinical reference, clinicians will find the up-to-date resources needed to effectively and confidently recognize, diagnose, and treat neurologic diseases and disorders in equine patients. The editors and authors have used their collective experience to produce a volume that integrates the necessary fundamental concepts into a clinical approach to the numerous afflictions of the nervous system of the horse.

- Organized into three complementary sections mirroring the problem-based approach necessary to treat disease
- A working tool and reference for clinicians, veterinary students, residents, and specialty clinicians
- Heavily referenced throughout allowing for further in-depth study

---

Martin Furr, DVM, PhD, Diplomate ACVIM, is Adelaide Riggs Chair of Internal Medicine, Chief of Medicine, and Professor of Medicine at the Marion duPont Scott Equine Medicine Center, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, USA.

Stephen Reed, DVM, Diplomate ACVIM, is former Professor and Head of Equine Medicine and Surgery at The Ohio State University College of Veterinary Medicine, USA. He is currently affiliated with Rood and Riddle Equine Hospital, Lexington, KY, USA.



Blackwell Publishing

Equine Neurology

Equine Neurology

Edited by
Martin Furr and
Stephen Reed



Martin Furr, DVM, PhD, Diplomate ACVIM, is Adelaide Riggs Chair of Internal Medicine, Chief of Medicine, and Professor of Medicine at the Marion duPont Scott Equine Medicine Center, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, USA.

Stephen Reed, DVM, Diplomate ACVIM, is former Professor and Head of Equine Medicine and Surgery at the Ohio State University College of Veterinary Medicine, USA. He is currently affiliated with Rood and Riddle Equine Hospital, Lexington, KY, USA.

©2008 Blackwell Publishing
All rights reserved

Blackwell Publishing Professional
2121 State Avenue, Ames, Iowa 50014, USA

Orders: 1-800-862-6657
Office: 1-515-292-0140
Fax: 1-515-292-3348
Web site: www.blackwellprofessional.com

Blackwell Publishing Ltd
9600 Garsington Road, Oxford OX4 2DQ, UK
Tel.: +44 (0)1865 776868

Blackwell Publishing Asia
550 Swanston Street, Carlton, Victoria 3053, Australia
Tel.: +61 (0)3 8359 1011

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Publishing, provided that the base fee is paid directly to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license by CCC, a separate system of payments has been arranged. The fee codes for users of the Transactional Reporting Service are ISBN-13: 978-0-8138-2519-9/2008.

Library of Congress Cataloging-in-Publication Data

Equine neurology / edited by Martin Furr and Stephen Reed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-0-8138-2519-9
ISBN-10: 0-8138-2519-9
1. Horses—Diseases. 2. Nervous system—Diseases. 3. Veterinary neurology. I. Furr, Martin. II. Reed, Stephen M.
[DNLM: 1. Central Nervous System Diseases—veterinary. 2. Horse Diseases—diagnosis. 3. Nervous System Diseases—veterinary. SF 959.N47 E64 2008]

SF959.N47E68 2008
636.1'08968—dc22

2007029162

The last digit is the print number: 9 8 7 6 5 4 3 2 1

Dedication

This work is dedicated to our families, who make the effort not only possible, but worthwhile.

Contents

Contributors ix
Preface xi
Acknowledgments xiii

Section I: Foundations of Clinical Neurology

1 Overview of Neuroanatomy 3
Jerry Masty

2 Cerebrospinal Fluid and the Blood–Brain Barrier 33
Martin Furr and Frank Andrews

3 Immunology of the Central Nervous System 47
Martin Furr

4 Pharmaceutical Considerations for Treatment of Central Nervous System Disease 55
Martin Furr

Section II: Clinical Equine Neurology

5 Neurologic Examination 65
Martin Furr and Stephen Reed

6 Differential Diagnosis and Management of Horses with Seizures or Alterations in Consciousness 77
Veronique Lacombe and Martin Furr

7 Differential Diagnosis of Equine Spinal Ataxia 95
Martin Furr and Stephen Reed

8 Differential Diagnosis and Management of Cranial Nerve Abnormalities 101
Bonnie Rush, Laurie Beard, and Martin Furr

9 Differential Diagnosis of Urinary Incontinence and Cauda Equina Syndrome 119
Martin Furr and Francesca Sampieri

10 Electrodiagnostic Evaluation of the Nervous System 127
Veronique Lacombe and Frank Andrews

11 Anesthetic Considerations for Horses with Neurologic Disease 149
Alison Smith

12 The Basics of Equine Neuropathology 157
John L. Robertson

Section III: Specific Disease Syndromes

13 Viral Diseases of the Nervous System 169
Lutz Goehring

14 Bacterial Infections of the Central Nervous System 187
Martin Furr

15 Equine Protozoal Myeloencephalitis 197
Martin Furr

16 Parasitic Infection of the Central Nervous System 213
Martin Furr

17 Clostridial Neurotoxins: Botulism and Tetanus 221
Martin Furr

18 Miscellaneous Infections of the Central Nervous System 231
Martin Furr

19 Neurodegenerative Disorders 235
Robert MacKay

20 Equine Hepatic Encephalopathy 257
Samuel Hurcombe

21 Electrolytes and Neurological Dysfunction in Horses 269
Samuel Hurcombe

22 Cervical Vertebral Stenotic Myelopathy 283
Stephen Reed, Barrie Grant, and Yvette Nout

23 Congenital Malformation of the Nervous System 299
Martin Furr

24 Central Nervous System Trauma 305
Yvette Nout

25 Disorders of the Peripheral Nervous System 329
Martin Furr

26 Equine Neurotoxic Agents and Conditions 337
Martin Furr

27 Hypoxic/Ischemic Encephalopathy in the Foal 357
Martin Furr

28 Miscellaneous Movement Disorders 365
Caroline Hahn

29 Stereotypic and Other Behavior Problems 373
M. D. Marsden

30 Miscellaneous Conditions 403
Martin Furr

Index 407

Contributors

Frank M. Andrews, DVM, MS, Dip ACVIM
University of Tennessee
College of Veterinary Medicine
Knoxville, TN

Laurie A. Beard, DVM, MS, Dip ACVIM
Kansas State University
College of Veterinary Medicine
Manhattan, KS

Martin Furr, DVM, Dip ACVIM, PhD
Marion duPont Scott Equine Medical Center
Virginia-Maryland Regional College of Veterinary Medicine
Leesburg, VA

Lutz Goehring, DVM, MS, PhD, Dip ACVIM
Colorado State University
College of Veterinary Medicine
Fort Collins, CO

Barrie D. Grant, DVM, MS, Dip ACVS
San Luis Rey Equine Hospital
Bonsall, CA

Caroline Hahn, DVM, MSc, PhD, Dip ECEIM, Dip ECVN, MRCVS
The University of Edinburgh
Royal (Dick) School of Veterinary Studies
Midlothian
UK

Samuel D. A. Hurcombe, BSc, BVMS
The Ohio State University
College of Veterinary Medicine
Columbus, OH

Veronique Lacombe, DVM, PhD, Dip ACVIM
The Ohio State University
College of Pharmacy
Columbus, OH

Robert J. MacKay, BVSc, PhD, Dip ACVIM
University of Florida
College of Veterinary Medicine
Gainesville, FL

M.D. Marsden, BSc, PhD
Director, MDM Equestrian
Dalkeith
Midlothian
Scotland

Jerry Masty, DVM, MS, PhD
The Ohio State University
College of Veterinary Medicine
Columbus, OH

Bonnie R. Rush, DVM, MS, Dip ACVIM
Kansas State University
College of Veterinary Medicine
Manhattan, KS

Yvette Nout DVM, MS, PhD, Dip ACVIM, Dip ACVECC
Dierenklinick Emmeloord
Emmerlord
The Netherlands

Stephen Reed DVM, MS, Dip ACVIM
Rood and Riddle Equine Hospital
Lexington, KY

John L. Robertson, VMD, PhD
Virginia Tech
Virginia-Maryland Regional College of Veterinary Medicine
Leesburg, VA

Francesca Sampieri, Dr. Med. Vet., MS, MRCVS
Pietrasanta, Italy

Alison A. Smith, DVM, Dip ACVA
Virginia Tech
Marion duPont Scott Equine Medical Center
Virginia-Maryland Regional College of Veterinary Medicine
Leesburg, VA

Preface

Interest in and recognition of equine neurologic disease has advanced in recent years to the point that it is a common part of clinical practice. The interest in equine neurology is represented by widespread continuing education articles and lectures, primary research reports, and clinical case presentations in the veterinary literature. Given that numerous chapters dedicated to equine neurologic disease can be found in large animal textbooks, it is fair to ask the question "Why an entire textbook dedicated to equine neurology?" It is the editors' opinion that even though there is a fairly large amount of information in print regarding equine neurologic disease, the topic has heretofore been treated in a rather fragmented and haphazard manner. Discussions about specific disease syndromes are important and informative, but to truly appreciate the elegance and subtlety of nervous system disease, a more integrative approach is necessary; hence we have produced *Equine Neurology*.

As working teachers and clinicians, we have used our collective experience to try and produce a volume that integrates the necessary fundamental concepts into a clinical approach to the numerous afflictions of the nervous system of the horse. The text is organized into three complementary sections that we believe approximate the problem-solving process necessary to resolve clinical problems. Section I discusses the foundations of clinical neurology that are necessary to understand any neurologic illness. This section includes chapters on neuroanatomy, the blood–brain barrier and cerebrospinal fluid, inflammation of the nervous system, and the use of pharmaceuticals for the treatment of central nervous system disease. Section II presents a discussion of various clinical problems that might be presented to a practitioner, with the focus being a method for evaluating the problem and constructing a list of potential rule-outs. This is the first step in the clinical evaluation of a clinical problem and will lead the reader to a discussion of specific clinical diagnoses that are found in Section III.

The book is intended as a working tool and reference for clinicians and veterinary students, as well as advanced students of equine neurology such as residents and specialty clinicians. It was our intent to provide a text that was encyclopedic in nature and well referenced, allowing the reader to do more in-depth study if necessary and to evaluate the veracity of the statements in the book based on the scientific validity of the source documents. While it is our hope and belief that we have succeeded overall, constraints of time and length do exist. We hope that all readers use this book, enjoy reading it, and, having done so, improve their knowledge of and confidence in the management of equine neurologic disease.

Dr. Martin Furr
Dr. Stephen Reed

Acknowledgments

This work is the culmination of many years of effort on the part of the editors and authors to understand the science of equine neurology and its application to benefit horses and horse owners. In this effort, we have been led by many individuals that pioneered the discipline, specifically Drs. Joe Mayhew and Alexander deLaHunta, who provided a foundation upon which all of us have followed and, hopefully, built upon. In addition Chapter 22, Cervical Vertebral Stenotic Myelopathy, is dedicated to Dr. Bagly for his work on the treatment of cervical compression which has been a benefit to many horses.

We would like to specifically thank the contributing authors for the time and effort they put into making this volume a reality. To produce such excellent chapters while consumed with the demands of clinical cases, teaching, and research is a true reflection of their commitment to scholarship. We would specifically like to thank Dr. Blair Meldrum for his close proofreading of Chapter 26, Equine Neurotoxic Agents and Conditions, and Drs. Peter Morresey and Bryan Waldridge for their input in proofreading the entire manuscript. Ms. Dede Andersen of Blackwell Publishing was invaluable to us in putting this work together, and her advice and support are appreciated.

I (MF) also would like to thank my co-editor, Dr. Stephen Reed, for his many years as a professional colleague, friend, and mentor to not only me, but the many veterinarians that have sought his advice regarding a case. Finally, I (MF) would like to thank my colleagues at the Marion DuPont Scott Equine Medical Center, Virginia-Maryland Regional College of Veterinary Medicine, for their support while I dedicated time to this effort.

Dr. Martin Furr
Dr. Stephen Reed

Section I:
Foundations of Clinical Neurology

1
Overview of Neuroanatomy

Jerry Masty

In order to evaluate a patient with a neurologic disorder, a basic understanding of the structure and function of the nervous system is necessary. The goal of this chapter is not to expose the reader to intricate, exacting, and perhaps daunting detail, but rather to present a basic overview of neuroanatomy. Intentionally keeping the anatomy confined to a few key topic areas will provide the basic framework for developing an initial grasp of the structure and function of the nervous system. A basic understanding of the nervous system from an anatomic and functional perspective can be gained by looking at the structure of the brain or spinal cord and answering three basic questions: What is it? Where is it? And what does it do? The information as presented should serve as a foundation for more detailed and in-depth study that is presented in various books devoted solely and entirely to the study of neuroanatomy.

ORGANIZATION OF THE NERVOUS SYSTEM

The nervous system is organized into central and peripheral divisions. The central system is composed of the brain and spinal cord that form a central axis of function located within the skull and vertebral column. The peripheral system is formed by neuronal cell processes that extend from the central axis to the periphery. There are also collections of cell bodies in the periphery that contribute to the components of the peripheral system. The autonomic nervous system is formed by the cells and their processes that innervate the viscera of the body. The components of the autonomic system show features common to both the central and peripheral system; for this reason, the autonomic system is frequently discussed as a separate entity of the nervous system.

DEVELOPMENT

The nervous system begins as a thickening of the embryonic layer identified as ectoderm. The initial growth of the neural ectoderm forms a thickened layer of cells identified as the neural plate. The neural groove is evident as a depression in the neural plate. As continued growth of the developing system occurs, neural folds develop at the margins of the neural plate caused by migration of the cells in a dorsal direction. Eventually, the neural folds meet and fuse at the dorsal midline, thereby forming a cylindrical structure identified as the neural tube. This simplified explanation of the formation of the neural tube is shown in Figure 1.1.

During neural tube formation, cells from the region of the neural folds pinch off and migrate throughout the developing embryo. These are the neural crest cells that differentiate to become various structures in the adult: spinal ganglia, sensory ganglia associated with some of the cranial nerves, autonomic ganglia associated with various body systems, and cells of the adrenal medulla.

Closure of the neural tube begins in the midsection of the developing embryo and progresses in a cranial and caudal direction. The opening at each end of the tube is identified as the neural pore. If complete closure of either neural pore is arrested during development, congenital malformations may be evident after birth. Failure of closure of the rostral neural pore results in the condition of anencephaly, which results in decreased formation of the cerebral hemispheres. In extreme conditions, the hemispheres

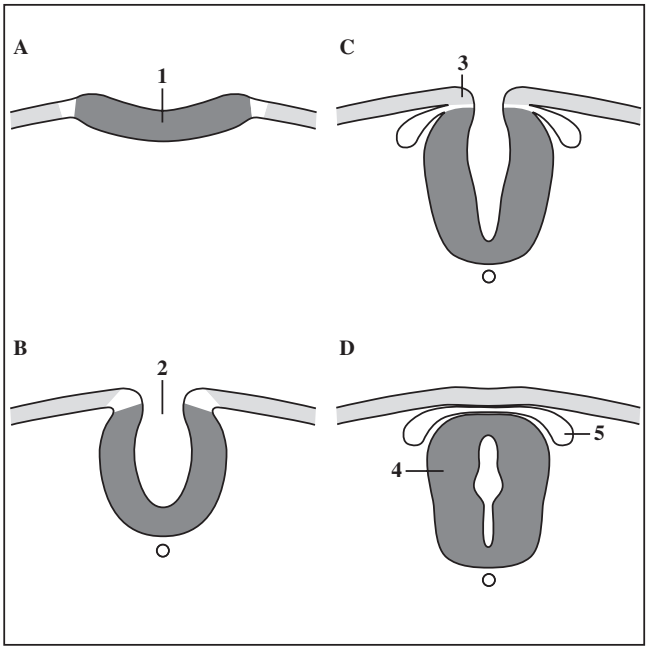


Figure 1.1. (A) Thickening of cells to form neural plate (1); (B) Indentation formed by the neural groove (2); (C) Closure of the neural tube produced by neural folds (3); (D) Neural tube (4); closure completed with formation of neural crest cells (5); Circle in B, C, D represents the notochord.

may be completely absent. Failure of closure of the caudal neuropore results in spina bifida. This condition presents as varying degrees of lack of closure and fusion of the neural tissue and the bony tissue of the vertebral canal that would normally enclose the caudal portion of the spinal cord.

To understand the basic generalized arrangement of the adult nervous system, certain facets of development should be kept in mind. As the neural tube completes its closure, it becomes a fluid-filled cylindrical structure that serves as the template for further development of the adult structures. Segments of the neural tube undergo differential growth to become the adult divisions and structures of the nervous system. As the process of differential growth occurs, the fluid-filled center of the embryonic neural tube follows this pattern of differential growth to become the ventricular system of the nervous system.

Embryonic Vesicles

The adult brain is divided into five regions that have their beginnings localized to specific areas of the developing neural tube. As the embryonic brain develops, it is characterized by vesicle formation (swellings) that begins to divide the developing brain topographically into separate regions. There is a primary stage of development where three vesicles are observed. This is followed by a secondary stage where five vesicles subsequently form from the initial three vesicles. Upon further differentiation and growth, the five vesicles observed in the secondary stage give rise to the five topographic regions of the adult brain.

From rostral to caudal, the vesicles of the primary stage are identified as the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). With continued differential growth at the rostral end of the neural tube, the prosencephalon develops into the telencephalon and diencephalon. At the caudal end of the tube, the rhombencephalon gives rise to the metencephalon and the more caudally positioned myelencephalon. Whereas the prosencephalon and rhombencephalon both develop into two adult divisions, the mesencephalon or midbrain remains as a single topographic region in the primary and secondary stages of development. The mesencephalon serves as the template for only a single adult division of the brain. This relationship is shown diagrammatically in Figure 1.2.

Ventricular System

The fluid-filled cavity of the developing neural tube follows the differential growth pattern of the neural tissue through the vesicle stages into the formation

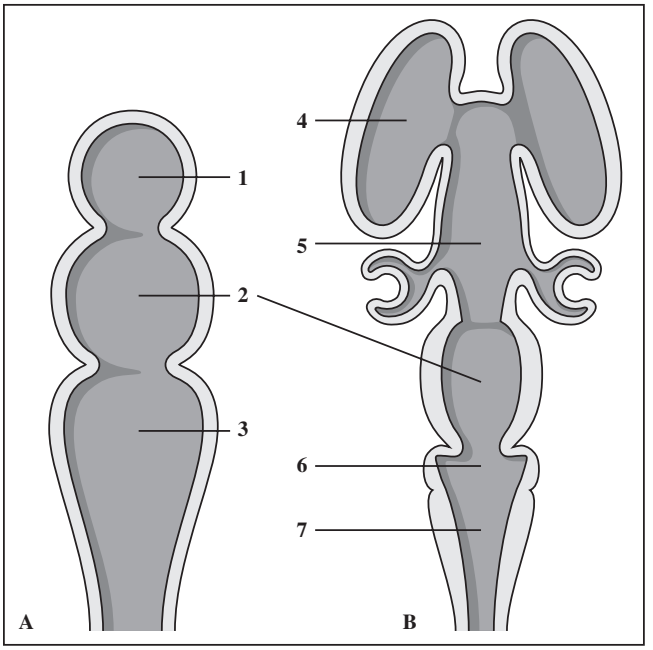


Figure 1.2. Embryonic brain vesicles. (A) Primary vesicle stage (B) Secondary vesicle stage
(1) Prosencephalon
(2) Mesencephalon
(3) Rhombencephalon
(4) Telencephalon
(5) Diencephalon
(6) Metencephalon
(7) Myelencephalon

of the adult brain. Therefore, a portion of the ventricular system is found at all levels of the adult brain as shown in Figure 1.3.

The right and left lateral ventricles follow the growth of the cerebral hemispheres of the telencephalon as they expand dorsally and caudally over the developing brainstem. The interventricular foramen interconnects each lateral ventricle with the third ventricle. The third ventricle, located in the diencephalon, is somewhat circular in shape. It encircles the interthalamic adhesion (the connection of the left and right halves of the thalamus across the midline of the brainstem). In the mesencephalon, the ventricular system is present as the tubular mesencephalic aqueduct. Cerebrospinal fluid produced in the lateral and third ventricles flows through the mesencephalic aqueduct to enter the relatively large fourth ventricle. The fourth ventricle is somewhat diamond shaped and overlies the metencephalon rostrally and the myelencephalon caudally. The lateral apertures of the fourth ventricle are located at the left and right ventricular margins at the approximate junction of the metencephalon with the myelencephalon. Cerebrospinal fluid leaves the fourth ventricle through the lateral apertures and enters the subarachnoid space that surrounds the brain and spinal cord. Cerebrospinal fluid can also enter the central canal of the spinal cord through the median aperture of the fourth ventricle at its caudal angle. The term obex is a topographic term that identifies the caudal angle of the fourth ventricle.

ORGANIZATION OF GRAY AND WHITE MATTER IN THE CENTRAL NERVOUS SYSTEM

The two main components of the central nervous system are the brain and the spinal cord. In turn, the brain and spinal cord are formed by neurons, their processes, and supporting tissues. Cell bodies of neurons and their nonmyelinated processes form the gray matter of the nervous system. White matter of the nervous system is formed by myelinated cell processes of the neurons. The gray and white matter of the nervous system is organized differently in the brain and spinal cord. Gray matter of the cerebrum is found either on its surface where it is identified as cortical gray matter or as collections of neuronal cell bodies located deep to the surface where they form subcortical clusters of gray matter. Neurons within a particular cluster generally perform the same function. When a cluster, or group, of neurons

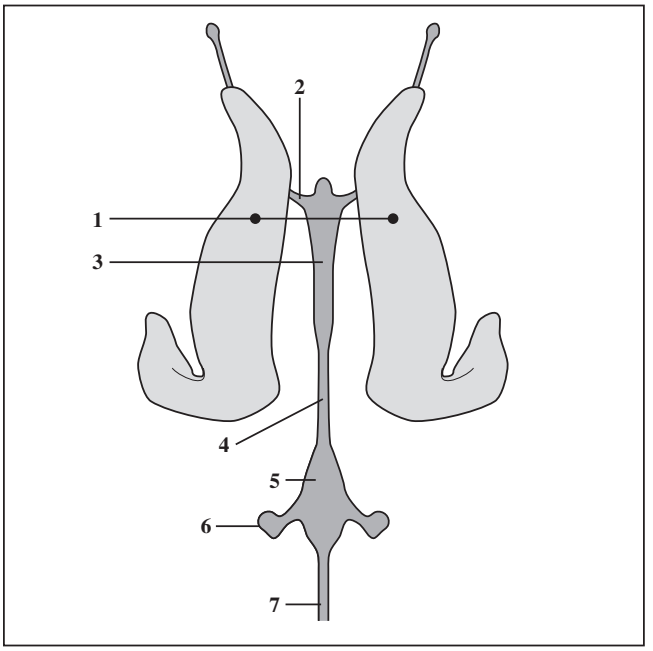


Figure 1.3. Dorsal view of ventricular system.
(1) Lateral ventricles
(2) Interventricular foramen
(3) Third ventricle
(4) Mesencephalic aqueduct
(5) Fourth ventricle
(6) Lateral aperture
(7) Extension of ventricular system into central canal of spinal cord

is located in the central nervous system, the collection of cell bodies is identified as a nucleus.

The white matter of the cerebrum is organized into bundles that form a system of conduction pathways in the cerebrum. The white matter of the cerebrum is divided into three types of white matter fiber systems consisting of projection fibers, commissural fibers, and association fibers. Projection fibers leave and enter the cerebrum to form connections with the brainstem and spinal cord. Commissural fibers carry information across the midline between the left and right cerebral hemispheres. There are two types of association fibers classified as either long or short fibers. The long association fibers carry information from one lobe of a cerebral hemisphere to another lobe on the same side of the cerebrum. Short association fibers carry information across adjacent gyri of the same cerebral lobe. Therefore, the long association fibers are also called interlobar fibers (passing between lobes); the short association fibers are also called intralobar fibers (confined to one lobe). A lobe of the brain refers to a region of the cortex that is named topographically for the overlying bone of the skull. Therefore, the frontal, parietal, occipital, and temporal lobes are identified deep to the skull bone of the same name.

The gray matter cell bodies forming various nuclei and white matter tracts are intermingled in each of the four remaining divisions of the brainstem. The arrangement of gray and white matter in the spinal cord has a topographic relationship. The cell bodies forming the gray matter of the spinal cord are arranged into the deeply located structures identified as the gray columns, or gray horns, of the spinal cord. The white matter is located superficial to the gray columns and is arranged into large bundles called funiculi as shown in Figure 1.4.

The columns of gray matter in the spinal cord are divided into the dorsal and ventral gray columns. In the thoracic and lumbar segments of the spinal cord, an additional column is present in a lateral position approximately midway between the dorsal and ventral columns. This lateral horn of gray matter contains cell bodies that function in the autonomic nervous system. Neuronal cells in the dorsal gray column are generally sensory in function, while neuronal cells in the ventral gray column are generally motor in function. The anatomic segregation of sensory and motor cells can be appreciated in the embryonic spinal cord as shown in Figure 1.5. The dorsal half of the developing gray matter is identified as the alar plate. Neurons in this region will become the sensory neurons in the dorsal gray

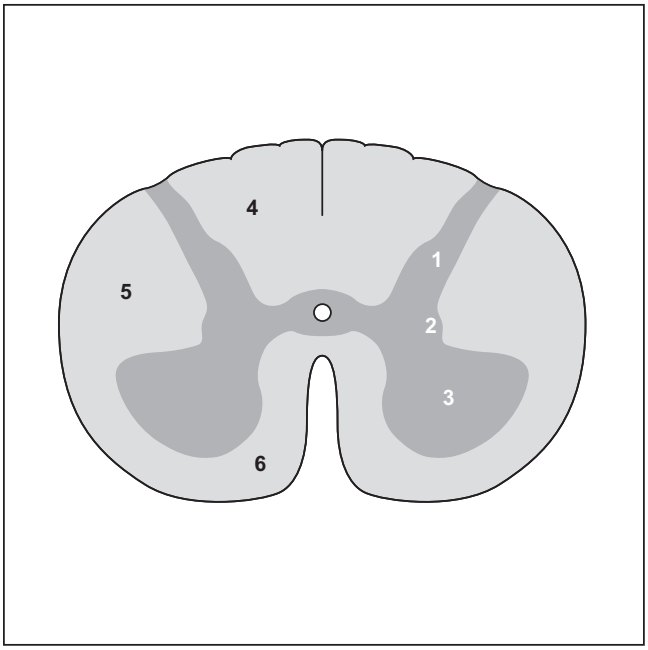


Figure 1.4. Arrangement of gray and white matter in the spinal cord. (1) Dorsal gray column; (2) Lateral gray column; (3) Ventral gray column; (4) Dorsal funiculus; (5) Lateral funiculus; (6) Ventral funiculus.

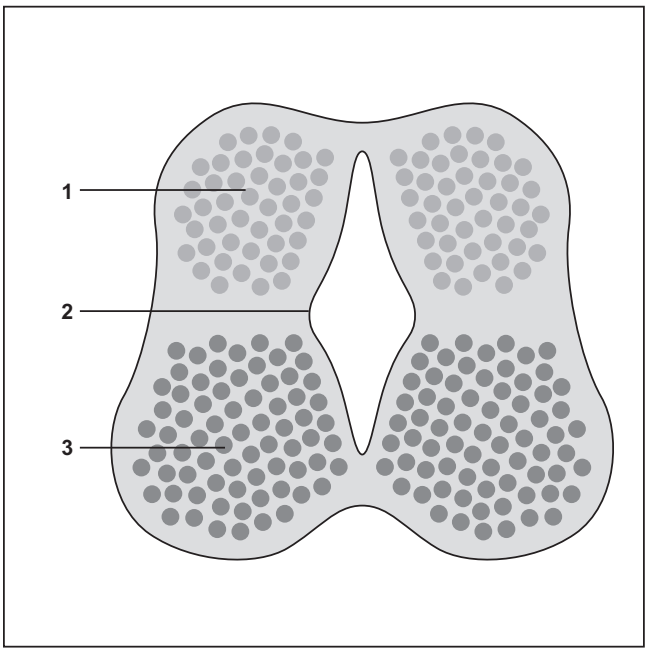


Figure 1.5. Neuron segregation in the developing spinal cord (schematic). (1) Alar plate containing sensory neurons; (2) Sulcus limitans; (3) Basal plate containing motor neurons.

column in the adult spinal cord. The ventral half of the gray matter is referred to as the basal plate. Neurons in this region will become the motor neurons in the ventral column of gray matter. The hollow portion of the embryonic tube will persist in the adult spinal cord as its central canal. There is a slight evagination within the central embryonic cavity identified as the sulcus limitans. Anatomically, the

sulcus limitans serves as a dividing line between the sensory and motor neurons of the developing spinal cord.

ORGANIZATION OF GRAY AND WHITE MATTER IN THE PERIPHERAL NERVOUS SYSTEM

Whereas the central nervous system is composed of the brain and spinal cord, the peripheral nervous system is composed of the ganglia and nerves located outside the central part of the system. By definition, a cluster of neuronal cell bodies located outside the central nervous system forms a ganglion. The ganglia constitute the major part of the gray matter in the peripheral system. Examples of the ganglia in the peripheral nervous system are ganglia that are associated with spinal and cranial nerves.

The white matter of the peripheral system is composed of nerve cell processes that travel throughout the body. Therefore, the white matter component of the peripheral nervous system is represented by the spinal and cranial nerves. The gray and white matter components of the autonomic nervous system will be described in the section on the anatomy of the autonomic nervous system.

AUTONOMIC NERVOUS SYSTEM: A TWO-CELL SYSTEM

The autonomic nervous system has anatomic features in common with both the central and peripheral divisions of the nervous system. The autonomic division of the nervous system is responsible for the neural regulation of the visceral functions of the body. The classical representation of the autonomic system divides the system into two functional components, the sympathetic and parasympathetic divisions of the autonomic system. The key point to understanding the anatomic arrangement of autonomic innervation is the realization that the system is represented by a model composed of two neurons that synapse on each other prior to innervating a target structure. The site of synapse occurs in ganglia discretely located within each of the respective functional divisions of the autonomic system. The targets of autonomic innervation are cardiac muscle, smooth muscle, and glands. Sympathetic and parasympathetic innervation of the same structure are usually antagonistic. The sympathetic nervous system prepares the body for the classic "fight or flight" response. Parasympathetic innervation promotes "rest and recovery" functions of the body.

Organization of the Sympathetic Nervous System

Sympathetic Preganglionic Cell Bodies

As stated above, sympathetic innervation is provided through a chained network of two neurons that synapse on each other in a ganglion prior to reaching the target of innervation. The first neuron in this chain is identified as the presynaptic, or preganglionic, neuron of origin for the sympathetic system. The preganglionic cell body is located in the lateral horn of the thoracic and lumbar segments of the spinal cord. For this reason, it is frequently said that the sympathetic nervous system has a thoracolumbar origin or is called the thoracolumbar division of the autonomic nervous system. The preganglionic nerve fiber, i.e., the axon of the preganglionic cell body, leaves the spinal cord to synapse on the second neuron in the chain identified as the postsynaptic, or postganglionic, cell body. The preganglionic neuron cell bodies can also be identified as the "first-order cell" in the chain of autonomic sympathetic innervation.

Sympathetic Postganglionic Cell Bodies

The sympathetic postganglionic cell body is located in one of the ganglia of the sympathetic division of the system where it receives the synaptic contact of the preganglionic fiber. Sympathetic ganglia can be classified into two main groups, either the prevertebral or paravertebral ganglia. A third group of sympathetic ganglia are not as well organized anatomically and can be defined as "other sympathetic ganglia."

Prevertebral sympathetic ganglia are positioned approximately along the midline ventral to the vertebral column. They are wrapped around the origins of the major abdominal blood vessels that come from the aorta. The prevertebral ganglia are the celiac ganglion, cranial mesenteric ganglion, and the caudal mesenteric ganglion. It is within these ganglia that the preganglionic axon synapses on the postganglionic cell body. In turn, the postganglionic cell body sends its axon into the periphery to reach the target of innervation.

The other main site of synapse for preganglionic sympathetic cells is in the paravertebral ganglia. These ganglia are located more laterally in relation to the position of the vertebral column. The paravertebral sympathetic ganglia are the cervical ganglia in the neck and the segmentally distributed ganglia along the sympathetic trunk in the thoracic and abdominal cavities. There are two pairs of cervical ganglia closely associated with the vagosympathetic trunk as it traverses the neck. The cranial cervical ganglia are located near the base of the skull. The middle cervical ganglia are located near the thoracic inlet. In the species of major veterinary interest, the caudal cervical ganglion has fused with the most cranial ganglion of the sympathetic trunk at the level of the first rib. This conjoined structure is identified as the cervicothoracic ganglion.

The third category of sympathetic ganglia is a miscellany of ganglia that are scattered along the aorta or are located near other organs. These ganglia can be identified individually as aortic ganglia, renal ganglia, and adrenal ganglia. A point of organizational detail regarding the sympathetic system that deserves some attention to detail is the path that the preganglionic fiber can take as it travels towards its ganglionic site of synapse with the second neuron in the chain. From its site of origin in the lateral horn of the spinal cord, the preganglionic fiber passes through the ventral root of the spinal nerve. At the level of the intervertebral foramen, the preganglionic fiber passes to the sympathetic trunk. At this point, there are four possibilities for the path of the preganglionic fiber as it travels to synapse with the postganglionic cell body in the chain. First, it can synapse at the level of the sympathetic trunk ganglia where it emerges from the spinal cord; second, it may traverse a few segments of the sympathetic trunk to synapse on a cranially located postganglionic cell body; third, it may likewise travel a few segments caudally to synapse on a postganglionic cell body; fourth, it may bypass the sympathetic trunk without synapsing on any of the sympathetic trunk neurons, rather it passes through the sympathetic trunk without synapse in order to synapse in one of the prevertebral ganglia. As the preganglionic fibers and postganglionic fibers pass between the sympathetic trunk and the spinal nerve, they form a stalk-like structure identified as the ramus communicans shown in Figure 1.6.

Preganglionic sympathetic fibers usually synapse on the postganglionic cell relatively near the target structures requiring autonomic innervation. In the

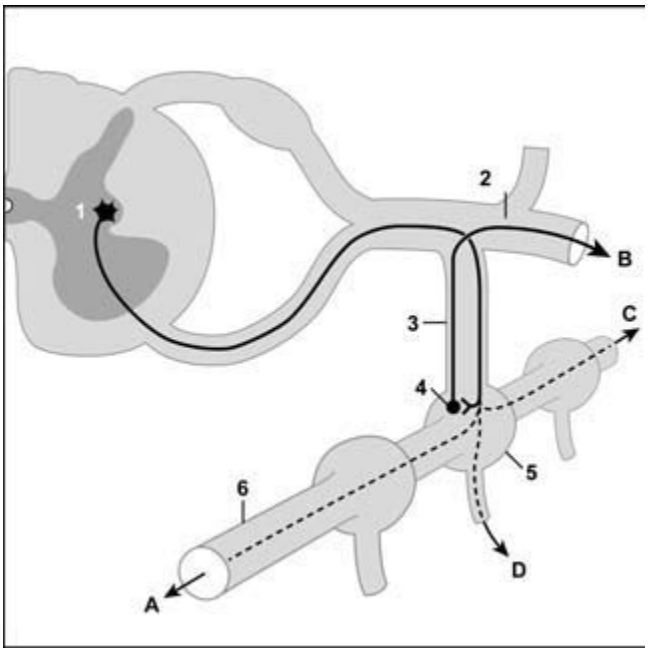


Figure 1.6. Model of sympathetic innervation. Preganglionic cells can synapse (A) on postganglionic cells a few segments cranial in the sympathetic trunk; (B) on a postganglionic cell at the segment where the postganglionic fiber emerges; (C) on a postganglionic cell caudal in the sympathetic trunk; (D) the preganglionic cell can bypass the sympathetic trunk ganglia and synapse in the prevertebral ganglia. (1) Preganglionic cell body; (2) Spinal nerve; (3) Ramus communicans; (4) Postganglionic cell body; (5) Sympathetic trunk ganglion; (6) Sympathetic trunk.

case of target structures in the head receiving sympathetic innervation, this becomes a relatively long pathway. From the preganglionic cell body in the lateral horn of the spinal cord, the preganglionic fiber travels through the ventral root of the spinal nerve, enters the sympathetic trunk, passes through the cervicothoracic ganglion and the ansa subclavia, through the middle cervical ganglion, through the vagosympathetic trunk in the cervical region, and finally reaches its site of synapse in the cranial cervical ganglion at the base of the skull. The postganglionic cells in the cranial cervical ganglion then send their postganglionic fibers to the target structures in the head such as the eye and salivary glands to provide sympathetic innervation. The sympathetic innervation scheme is shown in Figure 1.7.

Organization of the Parasympathetic Nervous System

The parasympathetic nervous system is also called the craniosacral division of the autonomic system. Anatomically, the parasympathetic system follows the two neuron chain model as described for the sympathetic system, but the preganglionic and postganglionic cell bodies are located in different parts of the nervous system. The term craniosacral indicates the location of the preganglionic parasympathetic cell bodies within the nervous system. Preganglionic parasympathetic cell bodies are found in nuclei associated with specific cranial nerves and in the sacral portions of the spinal cord. The postganglionic cell bodies are located in named ganglia associated with specific cranial nerves and in terminal ganglia throughout the body.

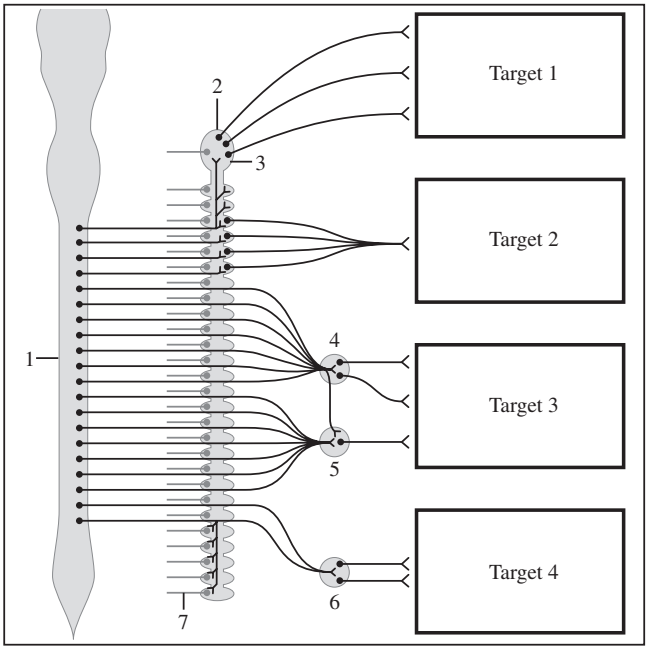


Figure 1.7. Sympathetic innervation targets. Structures receiving sympathetic innervation can be grouped as target areas in the body. Target 1 represents cranial structures such as ocular structures, the lacrimal gland and the salivary glands. Target 2 represents the thoracic viscera. Target 3 represents abdominal viscera. Target 4 represents urinary and pelvic viscera.
(1) Thoracolumbar origin of sympathetic innervation; (2) Sympathetic trunk; (3) Cervicothoracic ganglion; (4) Celiac ganglion; (5) Cranial mesenteric ganglion; (6) Caudal mesenteric ganglion; (7) Postganglionic sympathetic fibers to peripheral structures: vascular smooth muscle, arrector pili muscle, sweat glands.

Cranial Division: Parasympathetic Preganglionic Cell Bodies

In the cranial portion of the parasympathetic division, preganglionic parasympathetic cell bodies are associated with four cranial nerves, the oculomotor nerve (CN III), the facial nerve (CN VII), the glossopharyngeal nerve (CN IX), and the vagus nerve (CN X). Collections of preganglionic parasympathetic cells form nuclei that are associated with each of the four cranial nerves identified above. Each nucleus has an "anatomic" name and a "common" name, as shown in Table 1.1.

Table 1.1. Nuclei of the Parasympathetic Cranial Nerves. Note that the Parasympathetic Nucleus of the Facial Nerve Actually has Two Separate Components Identified by the Common Names of the Nuclei

Anatomic Name	Common Name
Parasympathetic nucleus of the oculomotor nerve	Edinger–Westphal nucleus
Parasympathetic nucleus of the facial nerve	Rostral salivatory nucleus
	Lacrimal nucleus
Parasympathetic nucleus of the glossopharyngeal nerve	Caudal salivatory nucleus
Parasympathetic nucleus of the vagus nerve	Dorsal vagal nucleus

Cranial Division: Parasympathetic Postganglionic Cell Bodies

The postganglionic cell bodies of three parasympathetic cranial nerves, the oculomotor nerve (CN III), the facial nerve (CN VII), and the glossopharyngeal nerve (CN IX), are located in named ganglia associated with those nerves. The postganglionic cell bodies for the vagus nerve (CN X) and the sacral component of parasympathetic innervation will be located in terminal ganglia, as summarized in Table 1.2. Terminal ganglia are autonomic ganglia located in the wall of the target structure. For example, the submucosal and myenteric ganglia of the intestinal tract represent collections of postganglionic cell bodies located in terminal ganglia.

Table 1.2. Named Ganglia Associated with Parasympathetic Postganglionic Nerve Cell Bodies

Cranial Nerve	Postganglionic Cell Body Location
Oculomotor (CN III)	Ciliary ganglion
Facial (CN VII)	Mandibular or pterygopalatine ganglion
Glossopharyngeal (CN IX)	Otic ganglion
Vagus (CN X)	Terminal ganglion

Sacral Division: Parasympathetic Sacral Preganglionic and Postganglionic Cell Bodies

The sacral division of the parasympathetic nervous system follows the same organizational model of a two-neuron chain as seen with the parasympathetic cranial division of the system. Preganglionic parasympathetic cell bodies are located in the lateral horn of the sacral spinal cord. Preganglionic fibers exit the sacral spinal cord and synapse in the pelvic ganglion or in terminal ganglia of the pelvic viscera (Figure 1.8).

TOPOGRAPHIC LANDMARKS OF THE BRAIN

An overview of the surface anatomy of the brain is described below. Readily observed structures of each of the five adult divisions of the brain will be highlighted. From caudal to rostral, the divisions of the brain are the myelencephalon, metencephalon, mesencephalon, diencephalon, and telencephalon. As each division is described, the reader should refer to the diagrams of the ventral surface of the brain (Figure 1.9), the dorsal surface of the brainstem (Figure 1.10), and the median section of the brain (Figure 1.11) to see the location of the referenced structures.

Myelencephalon

The myelencephalon is the most caudal part of the brainstem located between the trapezoid body cranially and the junction of the brainstem with the spinal cord at the level of the emergence of the first cervical spinal nerve. The ventral median fissure divides the ventral surface into right and left halves.

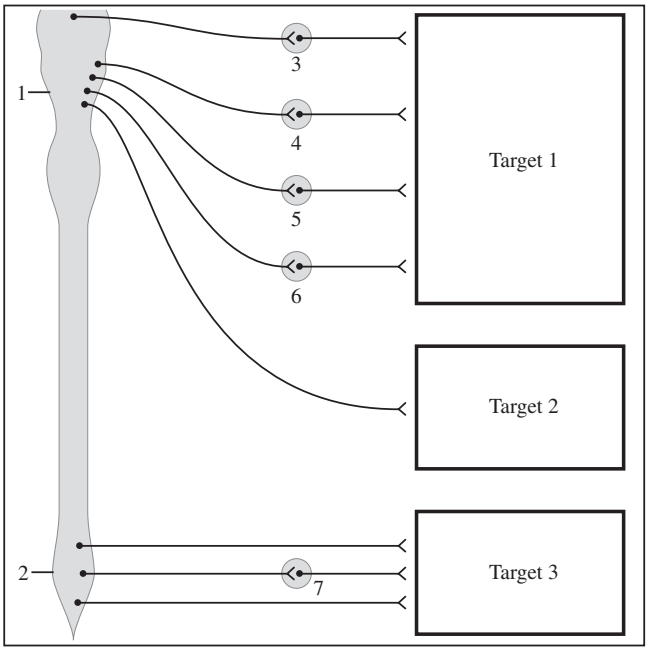


Figure 1.8. Parasympathetic innervation targets. Structures receiving parasympathetic innervation can be grouped as target areas in the body. Target 1 represents cranial structures such as ocular structures, the lacrimal gland and the salivary glands that are innervated by cranial nerves. Target 2 represents the thoracic and abdominal viscera that are innervated by the vagus nerve. Target 3 represents urinary and pelvic viscera that are innervated by the pelvic nerve. (1) Parasympathetic cranial nerve nuclei of origin in the brainstem; (2) Parasympathetic neurons in the sacral spinal cord; (3) Ciliary ganglion; (4) Pterygopalatine ganglion; (5) Mandibular ganglion; (6) Otic ganglion; (7) Pelvic ganglion.

Immediately adjacent to the fissure are the fiber bundles identified as the pyramids. The pyramids are motor fibers associated with the pyramidal motor system and represent descending fibers traveling through the brainstem. The rectangular shaped trapezoid body at the cranial edge of the myelencephalon is formed by fibers associated with the auditory system. The fibers of cranial nerves 6–12 exit the brainstem on the ventral surface of the myelencephalon.

Dorsal Myelencephalon

The caudal portion of the myelencephalon is closed dorsally, but the cranial portion of the dorsal myelencephalon is open where the fourth ventricle is located. Left and right halves of the myelencephalon are separated by the dorsal median sulcus. Three white matter fiber bundles occupy the dorsal surface. The bundle closest to the midline is the fasciculus gracilis (FG). The FG is formed by fibers that carry conscious proprioceptive impulses from the pelvic limb area of the body. Lateral to the FG is the fasciculus cuneatus (FC) which transmits conscious proprioceptive information from the thoracic limbs of the body. Moving laterally, the next bundle is the spinal tract of the trigeminal nerve. This tract is formed by fibers that carry nociceptive information from the head. The dorsal intermediate sulcus separates the FG and FC. The dorsolateral sulcus separates the FC from the spinal tract of the trigeminal nerve.

The caudal half of the fourth ventricle overlies the open cranial portion of the myelencephalon. The roof of the fourth ventricle, the caudal medullary velum, is formed by the thin layer of ependymal and pial cells of the meninges. The caudal angle of the fourth

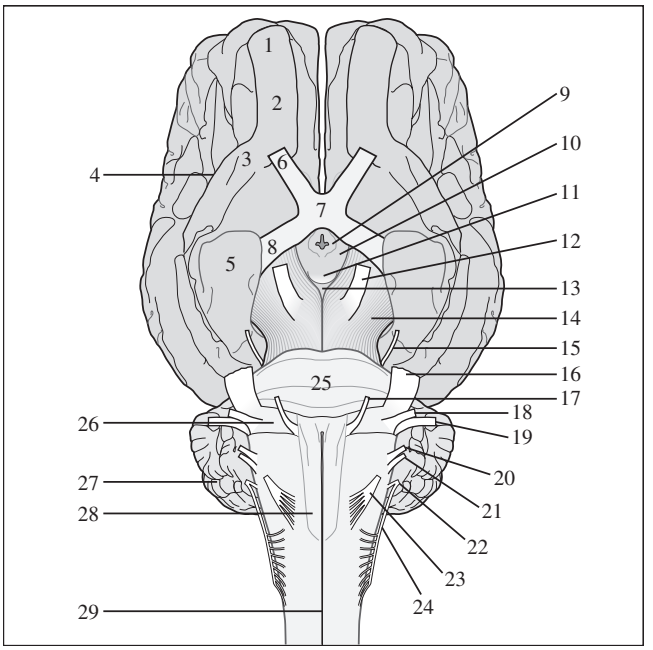


Figure 1.9. Ventral view of the brain (schematic). (1) Olfactory bulb; (2) Olfactory peduncle; (3) Lateral olfactory tract; (4) Lateral rhinal sulcus; (5) Piriform lobe; (6) Optic nerve; (7) Optic chiasm; (8) Optic tract; (9) Tuber cinereum; (10) Hypothalamus; (11) Mammillary body; (12) Oculomotor nerve; (13) Interpeduncular fossa; (14) Crus cerebri; (15) Trochlear nerve; (16) Trigeminal nerve; (17) Abducent nerve; (18) Facial nerve; (19) Vestibulocochlear nerve; (20) Glossopharyngeal nerve; (21) Vagus nerve; (22) Accessory nerve; (23) Hypoglossal nerve; (24) Spinal root of accessory nerve; (25) Transverse fibers of the pons; (26) Trapezoid body; (27) Cerebellum; (28) Pyramid; (29) Ventral median fissure.

ventricle forms a topographic landmark identified as the obex. The groove along the midline in the floor of the ventricle is the median sulcus. The sulcus limitans is the groove more lateral in position near the junction of the floor and wall of the ventricle.

Ventral Metencephalon

Moving rostrally, the next division of the brain is the metencephalon. The ventral surface is formed by the transverse fibers of the pons. This wide bundle of fibers transmits pyramidal motor information to the cerebellum. As the transverse fibers of the pons move laterally toward the dorsal surface of the metencephalon, they form the middle cerebellar peduncle which can be seen entering into the cerebellum. The longitudinal fibers of the pons, another fiber bundle of the pyramidal motor system, are located deep to the transverse fibers and cannot be seen on the ventral surface. The trigeminal nerve (CN V) leaves the ventral surface of the metencephalon at the rostral edge of the transverse fibers of the pons.

Dorsal Metencephalon

The cerebellum is the superstructure seen on the dorsal surface of the metencephalon. Three pairs of cerebellar peduncles connect the cerebellum to the brainstem. From lateral to medial, these stalk-like connections are identified as the middle, caudal, and rostral cerebellar peduncles respectively (Figure 1.10). The peduncles are named based on their connections to the brainstem, not on their position relative to each other. Therefore, the middle cerebellar peduncle is the most lateral of the three and has been described previously as fibers that represent the continuation of the transverse fibers of the pons carrying information

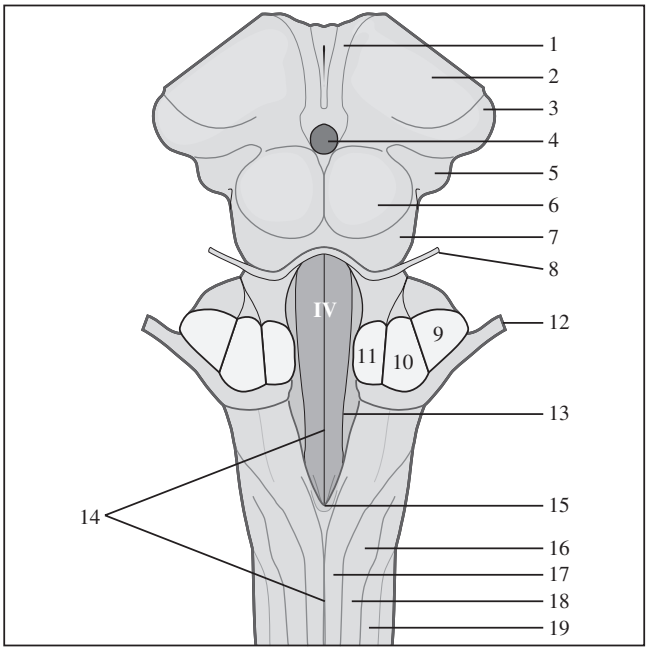


Figure 1.10. Dorsal view of the brainstem (schematic). (1) Stria habenularis thalami; (2) Thalamus; (3) Lateral geniculate body; (4) Pineal body; (5) Medial geniculate body; (6) Rostral colliculus; (7) Caudal colliculus; (8) Trochlear nerve; (9) Middle cerebellar peduncle; (10) Caudal cerebellar peduncle; (11) Rostral cerebellar peduncle; (12) Vestibulocochlear nerve; (13) Sulcus limitans; (14) Median sulcus; (15) Obex; (16) Cuneate tubercle; (17) Fasciculus gracilis; (18) Fasciculus cuneatus; (19) Spinal tract of the trigeminal nerve.

into the cerebellum. The caudal cerebellar peduncle is so named because it is formed by various tracts that pass through the caudal portion of the brainstem to reach the cerebellum. The most medial of the cerebellar peduncles is the rostral cerebellar peduncle. It is formed primarily by fibers originating in the cerebellum that travel rostrally into the brainstem. As a general rule of thumb, the caudal cerebellar peduncle carries a majority of fibers that represent afferent tracts entering the cerebellum; likewise, the rostral cerebellar peduncle in general carries fibers that represent efferent tracts leaving the cerebellum. The rostral portion of the fourth ventricle overlies the metencephalon. The roof of the fourth ventricle in this location is formed by the thin layer of ependymal and pial cells of the meninges identified as the rostral medullary velum.

Ventral Mesencephalon

The third division of the brain is the mesencephalon, also called the midbrain. The crus cerebri are conspicuous fiber bundles on the ventral surface. These relatively large bundles are formed by fibers of the pyramidal motor system as they pass through the mesencephalon to reach caudal portions of the brainstem. The interpeduncular fossa is the space between the left and right crus cerebri. The oculomotor nerve (CN III) emerges from the ventral surface of the mesencephalon.

Dorsal Mesencephalon

The dorsal surface of the mesencephalon is characterized by two pairs of rounded prominences, the rostral and caudal colliculi. Each rostral colliculus serves as a synaptic site in the pathway for visual reflexes. The caudal colliculus serves as a synaptic site in the pathway for auditory reflex activity. The mesencephalic aqueduct is that part of the ventricular system located in the mesencephalon. It interconnects the third and fourth ventricles.

The trochlear nerve (CN IV) emerges from the dorsal surface of the mesencephalon and turns

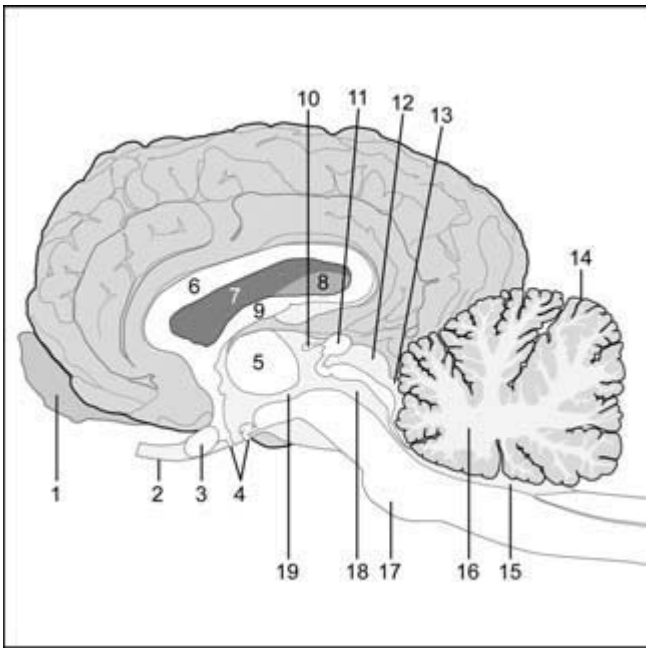


Figure 1.11. Median section of the brain (schematic). (1) Olfactory bulb; (2) Optic nerve; (3) Optic chiasm; (4) Hypothalamus (pituitary gland removed); (5) Interthalamic adhesion; (6) Corpus callosum; (7) Lateral ventricle; (8) Hippocampus; (9) Fornix; (10) Habenula; (11) Pineal body; (12) Rostral colliculus; (13) Caudal colliculus; (14) Cerebellum; (15) Fourth ventricle; (16) Arbor vitae (cerebellar white matter); (17) Pons; (18) Mesencephalic aqueduct; (19) Third ventricle.

ventrolaterally to reach the ventral surface of the brainstem as it travels toward the orbit. The trochlear nerve is the only cranial nerve that originates from the dorsal surface of the brainstem.

Ventral Diencephalon

The most rostral extent of the brainstem is the diencephalon. The diencephalon is composed of five separate parts: thalamus, epithalamus, metathalamus, hypothalamus, and subthalamus. Parts of these divisions of the diencephalon are visible on the ventral, dorsal, and lateral surfaces of the diencephalon.

The ventral surface of the diencephalon is formed by the hypothalamus. The mammillary body caudally and the optic chiasm rostrally demarcate the boundaries of the hypothalamus. The pituitary gland is attached to the tuber cinereum, a slightly elevated ridge of hypothalamic tissue between the two landmarks identified above. The mammillary body appears as a small prominence and is the most caudally located structure of the ventral surface of the diencephalon. The mammillary body is a relay station interconnecting olfactory, behavioral, and autonomic areas of the brain. The optic nerve (CN II) fibers enter at the rostral edge of the diencephalon and form the optic chiasm.

Dorsal Diencephalon

The dorsal surface of the diencephalon is visible after the cerebrum has been removed. The left and right lateral geniculate bodies are dorsocaudal projections at the caudal most margin of the thalamus. The lateral geniculate bodies are relay stations that send visual information into the cerebrum. Slightly ventral to each lateral geniculate body is the medial geniculate body on either side of the diencephalon. The medial geniculate bodies are relay stations that send auditory information to the cerebrum. The metathalamus, one of the five divisions of the diencephalon, is formed by both the lateral and medial geniculate bodies.

The epithalamus is the division of the diencephalon that is located dorsal to the thalamus. The structures of the epithalamus are the paired bundles of the stria habenularis thalami that connect cerebral and hypothalamic structures to a nuclear area of the epithalamus identified as the habenular nucleus, of the habenula, a small prominence near the dorsocaudal limit of the epithalamus. The small unpaired prominence caudal to the habenula at the midline is the pineal body.

The third ventricle lies along the median plane at the level of the diencephalon. The left and right divisions of the thalamus are joined across the midline by thalamic tissue identified as the massa intermedia or interthalamic adhesion. A midsagittal view of the brainstem reveals the interthalamic adhesion as the circumscribed area in Figure 1.11. The third ventricle encircles the interthalamic adhesion.

Ventral Telencephalon

The telencephalic vesicle in the developing embryo gives rise to the cerebrum formed by the left and right cerebral hemispheres. The cerebrum is the large superstructure that is connected to and covers the rostral brainstem. On the ventral surface, the olfactory bulbs are located at the rostral limit of each hemisphere. Olfactory receptors located in the nasal cavity transmit impulses along the olfactory nerve (CN I) to synapse in the olfactory bulbs. The olfactory tract is visible on the ventral surface in its position between the olfactory bulbs and the piriform lobe of the cerebrum. These olfactory structures contribute to the formation of that part of the cerebrum identified as the rhinencephalon for processing olfactory information. The rhinencephalon is demarcated from the rest of the cerebral cortex by the lateral rhinal sulcus.

The surface of the cerebrum is characterized by ridges identified as gyri and grooves identified as sulci. The left and right cerebral hemispheres are separated along the midline by the longitudinal cerebral fissure. The caudal aspect of each hemisphere is separated from the cerebellum by the transverse cerebral fissure. The surface of the cerebrum is divided into lobes that are named topographically for the overlying bone of the skull. The cerebral lobes are therefore identified as frontal, parietal, temporal, and occipital. Different neural functions are associated with each of the lobes. A greatly simplified listing of cerebral function makes the following associations: the frontal lobe is associated with motor activity; the parietal lobe is the association area; auditory information is processed in the temporal lobe; and the occipital lobe processes visual information.

The left and right lateral ventricles are contained within each respective cerebral hemisphere. They intercommunicate at the midline with the third ventricle through the interventricular foramen. The olfactory nerve (CN I) synapses on the ventral surface at the olfactory bulb.

TOPOGRAPHIC FEATURES OF THE SPINAL CORD

The spinal cord is divided into left and right halves by the dorsal median sulcus and the ventral longitudinal fissure as shown in Figure 1.12. The spinal cord is composed of gray and white matter, with the white matter superficial to the deeper embedded gray matter. Large bundles of white matter in the spinal cord are identified as funiculi. Each funiculus in turn is formed by smaller bundles of white matter, identified as the various ascending or descending tracts of the spinal cord. Spinal nerve roots enter and leave the spinal cord dividing it in a segmental manner.

The left and right dorsal roots enter the spinal cord at the dorsolateral sulcus. The left and right dorsal funiculus is the large bundle of white matter located between the dorsal roots. Each dorsal funiculus is further divided by the intermediate sulcus. The FG is located between the intermediate sulcus and the dorsal median sulcus. It carries information related to conscious proprioception from the pelvic limb area of the body. The FC is located between the intermediate sulcus and the dorsal root. This fiber bundle of the dorsal funiculus carries information related to conscious proprioception from the thoracic limb area of the body. Fibers located in the very lateral margin of the FC are actually fibers of the cuneocerebellar tract (CCT) that transmit unconscious proprioceptive information from the thoracic limb area. There are no grossly visible grooves that demarcate the CCT from the FC. Fibers located in the dorsal funiculus of the spinal cord are predominately fibers for conscious proprioception, with a small component for unconscious proprioception.

The lateral funiculus is the large bundle of white matter located between dorsal and ventral roots on either half of the spinal cord. Each lateral funiculus is formed by a mixture of ascending and descending tracts as shown in Figure 1.13.

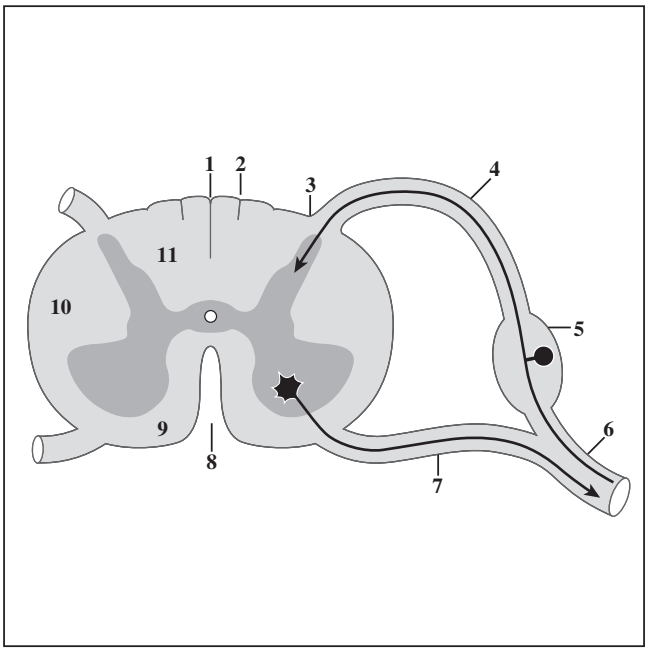


Figure 1.12. Spinal cord cross section (schematic). The fiber of a sensory neuron is shown as it enters the spinal cord through the dorsal root. The fiber of a motor neuron is shown as it leaves the spinal cord through the ventral root. (1) Median sulcus; (2) Dorsal intermediate sulcus; (3) Dorsolateral sulcus; (4) Dorsal root; (5) Spinal ganglion; (6) Spinal nerve proper; (7) Ventral root; (8) Ventral median fissure; (9) Ventral funiculus; (10) Lateral funiculus; (11) Dorsal funiculus.

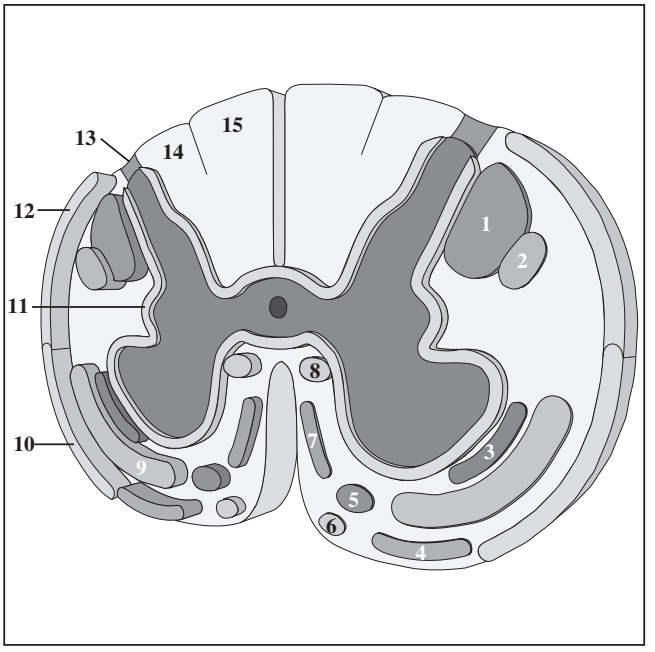


Figure 1.13. Position of ascending and descending tracts in the spinal cord (schematic). Descending tracts are numbered on the right; ascending tracts are numbered on the left. (1) Lateral corticospinal tract; (2) Rubrospinal tract; (3) Medullary reticulospinal tract; (4) Lateral vestibulospinal tract; (5) Pontine reticulospinal tract; (6) Tectospinal tract; (7) Ventral corticospinal tract; (8) Medial longitudinal fasciculus; (9) Spinothalamic tract; (10) Ventral spinocerebellar tract; (11) Fasciculus proprius (contains ascending and descending fibers); (12) Dorsal spinocerebellar tract; (13) Dorsolateral fasciculus (Lissauer's tract); (14) Fasciculus cuneatus; (15) Fasciculus gracilis.

The ventral funiculus is located between the ventral roots. It is also formed by a mixture of ascending and descending tracts.

FUNCTIONALITY OF THE SPINAL CORD

The white matter of the spinal cord is formed by ascending and descending pathways that transmit sensory and motor information through the nervous system. As a general rule, ascending pathways originate in the spinal cord and travel to higher levels in the brain. Analogously, descending pathways that regulate motor activity originate in higher levels of the brain and descend through the central nervous system to reach spinal cord levels.

Somatic Sensory Pathways in the Spinal Cord

There are two generalized principal sensory systems of the body, a system responsible for detecting the sense of body position and a system responsible for detecting the sensation of pain. These two sensations are defined as proprioception and nociception respectively. Six major pathways that monitor proprioception and the classic pathway for nociception are described below.

General Proprioception

Each main area of the body utilizes a different pathway for the conduction and organization of proprioceptive impulses. The proprioceptive pathways serving the body can be further divided into those which conduct impulses from either the pelvic limb area or the thoracic limb area. Detection of body movement and position (proprioception) is relayed to higher centers where it can reach a state of conscious perception or remain at an unconscious level. The conscious proprioception system monitors limb position while the animal is stationary and the unconscious system monitors proprioception when the animal in motion.

The pathways for proprioception are formed by a chain of neurons with synapses at specific levels of the nervous system. For conscious proprioception, three neurons are in the chain. For unconscious proprioception, there are only two neurons in the chain. The cell body of the first-order neuron in both the conscious and unconscious pathway is located in the spinal ganglia. For conscious proprioception, the cell body of the second-order neuron is located in the myelencephalon. The third-order neuron in the conscious proprioceptive pathway is in the ventral caudolateral nucleus (VCL) of the thalamus. With one exception, the CCT, the second-order neuron for unconscious proprioception is located in the dorsal column of gray matter in the spinal cord.

The relay pathways for proprioception from the body can be organized into pathways that carry information for both conscious and unconscious proprioception. For the pelvic limb, the conscious pathway is the FG; there are two unconscious pelvic limb pathways, the dorsal spinocerebellar tract (DSCT) and the ventral spinocerebellar tract (VSCT). The conscious proprioceptive pathway that serves the thoracic limb is the FC; there are also two unconscious pathways serving the thoracic limb, the CCT and the rostral spinocerebellar tract (RSCT).

Pelvic Limb—Conscious Proprioception

The cell bodies of the neurons that are responsible for detecting proprioceptive changes are located in the spinal ganglia. The dendrites of these neurons are modified to function as proprioceptors. The axons of the first-order cells project as part of the dorsal root of the spinal nerve and enter the white matter of the dorsal funiculus. As these axons turn and pass cranially through the spinal cord, they form the discrete fiber tract identified as the FG which lies immediately adjacent to the dorsal midline. These fibers ascend ipsilaterally until they reach their site of synapse in the myelencephalon. A synapse occurs in the nucleus gracilis located at the approximate level of the obex. The neurons in this nucleus are the second-order neurons in this conscious proprioceptive pathway. As the second-order axons cross the midline of the brainstem, they form the deep arcuate fibers. These fibers turn rostrally and ascend in the brainstem as a component of a fiber bundle known as the medial lemniscus. The synapse with the third-order neuron occurs in the VCL nucleus of the thalamus. These third-order neurons send their axons ipsilaterally through the internal capsule to their termination in the somesthetic cerebral cortex. This pathway is schematically shown in Figure 1.14.

Pelvic Limb—Unconscious Proprioception

Unconscious proprioceptive information is relayed to the cerebellar cortex. Two pathways are involved in the transmission of this information from

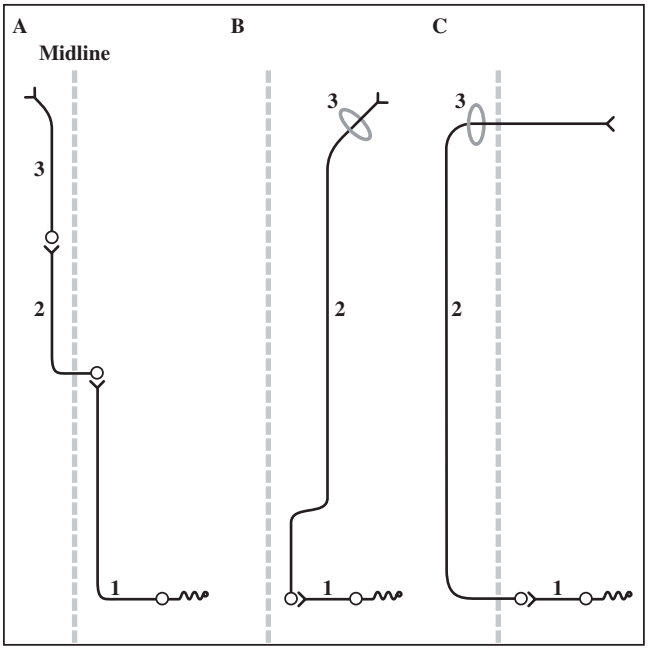


Figure 1.14. Schematic representation of pelvic limb proprioceptive pathways. Dotted line represents the midline of the spinal cord in A, B, and C. See text for complete description. (A) Fasciculus gracilis. (1) First order neuron with cell body (circle) in spinal ganglion. Axon forms the ipsilateral fasciculus gracilis. (2) Second order neuron with cell body (circle) in the nucleus gracilis. Axon crosses the midline as deep arcuate fibers and ascends contralaterally as part of the medial lemniscus. (3) Third order neuron with cell body (circle) in the VCL nucleus. Axon ascends through the internal capsule to the cerebral cortex. (B) Dorsal spinocerebellar tract. (1) First order neuron with cell body (circle) in the spinal ganglion. Axon synapses in ipsilateral dorsal gray column. (2) Second order neuron with cell body (circle) in the dorsal gray column. Axon forms the ipsilateral dorsal spinocerebellar tract. (3) Oval represents the caudal cerebellar peduncle through which the second order axons pass to reach the cerebellar cortex. (C) Ventral spinocerebellar tract. (1) First order neuron with cell body (circle) in the spinal ganglion. Axon synapses in ipsilateral dorsal gray column. (2) Second order neuron with cell body (circle) in dorsal gray column. Axon decussates and ascends contralaterally forming the contralateral ventral spinocerebellar tract. (3) Oval represents the rostral cerebellar peduncle through which second order axons enter the cerebellum and decussate to synapse in the cerebellum.

the pelvic limb area of the body: the DSCT and the VSCT. The first-order neuron cell bodies are located in the spinal ganglia. Their axons enter the spinal cord and will synapse in a discrete area of the dorsal gray column identified as the nucleus of the DSCT, more commonly referred to as the thoracic nucleus. Axons from these second-order neurons enter the ipsilateral lateral funiculus and ascend in the spinal cord as the DSCT. The axons enter the caudal cerebellar peduncle to synapse in the cerebellar cortex as shown in Figure 1.14.

The VSCT also carries unconscious proprioceptive information from the pelvic limb area to the cerebellar cortex through a slightly different pathway. First-order cell bodies are also located in the spinal ganglion. The first-order axons enter the dorsal gray column and synapse on the lateral aspect of its base. The second-order axons cross through the

ventral white commissure and ascend without synapse contralaterally to the level of the rostral cerebellar peduncle. These axons recross in the cerebellum prior to reaching their site of synapse in the cerebellar cortex as depicted in Figure 1.14.

Thoracic Limb—Conscious Proprioception

The arrangement of fibers conveying conscious proprioception from the thoracic limb area is similar to that of the pelvic limb. First-order neuron cell bodies are located in the spinal ganglia. Their axons enter the dorsal funiculus and form the FC located immediately lateral to the FG. The first synapse in this pathway occurs in the medial cuneate nucleus located in the myelencephalon. The second-order axons immediately decussate, contribute to the formation of the deep arcuate fibers, and pass rostrally within the medial lemniscus. They will synapse in the VCL nucleus on the third-order neurons. From here, proprioceptive information reaches the somesthetic cortex via the internal capsule as did the fibers of the FG. This pathway is shown in Figure 1.15.

Unconscious Proprioception—Thoracic Limb

Just as there are two pathways for unconscious proprioception from the pelvic limb area of the body, there are also two pathways serving the thoracic limb region of the body, the CCT and RSCT. The first-order neuron cell bodies of the CCT are located in the spinal ganglia. The first-order axons travel in the lateral aspect of the FC to their site of synapse in the lateral cuneate nucleus. The second-order axons from the lateral cuneate nucleus project to the cerebellar cortex through the ipsilateral caudal cerebellar peduncle as shown in Figure 1.15.

The other unconscious pathway from the thoracic limb region is the RSCT. The first-order neuron cell bodies are also located in the spinal ganglia. First-order axons enter the dorsal gray column and synapse with second-order neurons. The second-order axons enter the ipsilateral lateral funiculus and project to the cerebellar cortex through both the rostral and caudal cerebellar peduncles as depicted in Figure 1.15.

Spinal Nociception

Fibers carrying impulses related to touch and noxious stimuli form the spinothalamic tract (ST) as they ascend through the spinal cord. Fibers of the lateral spinothalamic tract in the lateral funiculus and fibers from the ventral spinothalamic tract in the ventral funiculus form a ventrolateral system for pain transmission. The lateral ST tract is the classic pain pathway in primates and will serve as the classic model for this modality in animals of major veterinary interest. Pain transmission in the domestic species differs in that is multisynaptic with numerous ipsilateral and contralateral interconnections compared to the classic primate pathway described below.

The first-order neuron is located in the spinal ganglion. First-order axons ascend and descend in the cord traversing short intersegmental distance prior to their synapse. These fibers form the dorsolateral fasciculus present throughout the spinal cord. The first-order axons then enter the gray matter of the dorsal horn to synapse on the cell body of the second-order neuron in the pathway. Second-order axons immediately cross to the opposite side and form the lateral corticospinal (LCS) tract in the contralateral funiculus. At the level of the diencephalon, a synapse occurs on the third-order neuron in the VCL nucleus of the thalamus. Third-order axons enter into the formation of the internal capsule as they travel to their respective site of synapse in the somesthetic cortex.

DESCENDING TRACTS OF THE SPINAL CORD

The descending tracts of the spinal cord are shown opposite the ascending tracts in Figure 1.13. These tracts provide a descending regulatory motor influence (usually inhibitory) on other motor neurons located in the brain and spinal cord. Neurons of the motor system send their axons from higher levels of the central nervous system to regulate and influence the activity of the motor cells that leave the central nervous system to innervate target structures in the periphery. Neurons in the higher levels of the central nervous system are defined as upper motor neurons. Neurons that send their axons to provide motor innervation to peripheral targets are defined as lower motor neurons. The descending tracts of the spinal cord are formed by axons of upper motor neurons that descend through the brain and spinal cord to provide a regulatory influence on the lower motor cells. The upper motor system is organized into two components, the pyramidal motor system

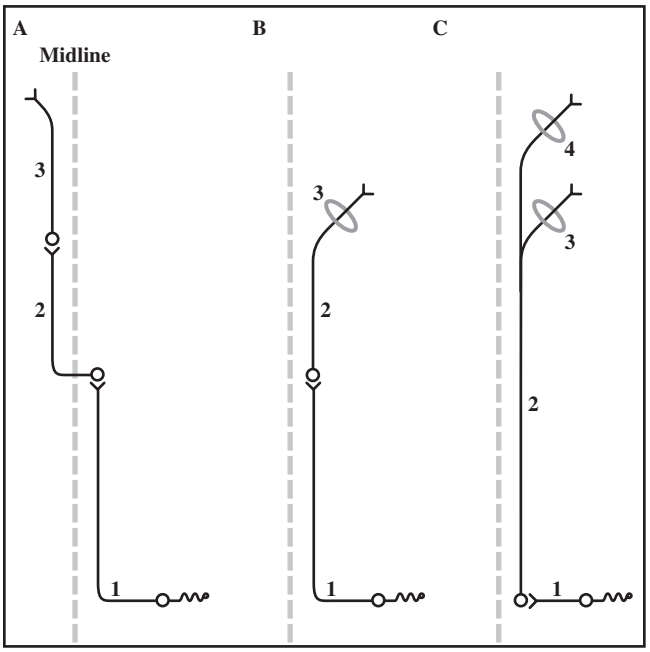


Figure 1.15. Schematic representation of thoracic limb proprioceptive pathways. Dotted line represents the midline of the spinal cord in A, B, and C. See text for complete description. (A) Fasciculus cuneatus. (1) First order neuron with cell body (circle) in spinal ganglion. Axon ascends ipsilaterally forming the fasiculus cuneatus. (2) Second order neuron with cell body (circle) in the medial cuneate nucleus. Axon crosses the midline as deep arcuate fibers and ascends contralaterally as part of the medial lemniscus. (3) Third order neuron (circle) with cell body in the VCL nucleus. Axon ascends through the internal capsule to the cerebral cortex; (B) Cuneocerebellar tract. (1) First order neuron with cell body (circle) in spinal ganglion. Axons ascends ipsilaterally as the cuneocerebellar tract. (2) Second order neuron with cell body (circle) in lateral cuneate nucleus. Axon enters the cerebellum through the caudal cerebellar peduncle (3). (C) Rostral spinocerebellar tract. (1) First order neuron with cell body (circle) in spinal ganglion. (2) Second order neuron with cell body (circle) in the dorsal gray column. Axon ascends ipsilaterally as the rostral spinocerebellar tract to enter the cerebellum through the caudal cerebellar peduncle (3) and the rostral cerebellar peduncle (4).

and the extrapyramidal system. From an anatomic viewpoint, the pyramidal system part of the motor system is more discretely organized than the extrapyramidal division.

Pyramidal Motor Organization

Pyramidal motor neurons are located near the cruciate sulcus of the cerebral cortex. The function of the pyramidal system is to provide regulatory control of motor activities that require a high degree of skilled movement. Therefore, this system is of greater relative importance in primates than in the species usually treated by the veterinary practitioner. The axons from the pyramidal motor cell bodies descend through the higher levels of the brain as they travel to synapse on lower motor neurons located in other regions of the brainstem and the spinal cord. They contribute to the formation of various white matter structures of the cerebrum, brainstem, and spinal cord. There are three distinct pyramidal motor tracts formed by the descending fibers: the corticopontine, corticonuclear, and corticospinal tracts. The

path formed by the pyramidal fibers is shown in Figure 1.16. Axons of all three tracts contribute to the white matter that forms the corona radiata and internal capsule in the cerebrum and the crus cerebri at the level of the mesencephalon.

At the level of the metencephalon, fibers of the corticopontine tract synapse in the pontine nucleus. Axons from the pontine nucleus ascend contralaterally and form the middle cerebellar peduncle as they enter the cerebellum to synapse in the cerebellar cortex. This pathway provides pyramidal motor input into the cerebellum, thereby aiding in regulation of motor activity.

The remaining two fiber bundles of the pyramidal system, the corticonuclear and corticospinal fibers, continue their caudally directed descent through the nervous system. The corticonuclear fibers synapse on lower motor nuclei of various cranial nerves in the brainstem. The corticonuclear fibers exert a regulatory influence on cranial nerves that provide lower motor innervation to target structures in the head.

The remaining fibers that descend into the spinal cord form the lateral and ventral corticospinal tracts. These fibers are grossly visible on the ventral surface of the myelencephalon as the pyramids and give rise to the name of this division of the motor system. As the corticospinal fibers reach the caudal part of the pyramid, the majority of fibers synapse to descend contralaterally into the spinal cord. The crossing of fibers from one side to the other forms the pyramidal decussation. These fibers form the LCS tract located in the lateral funiculus of the spinal cord seen in

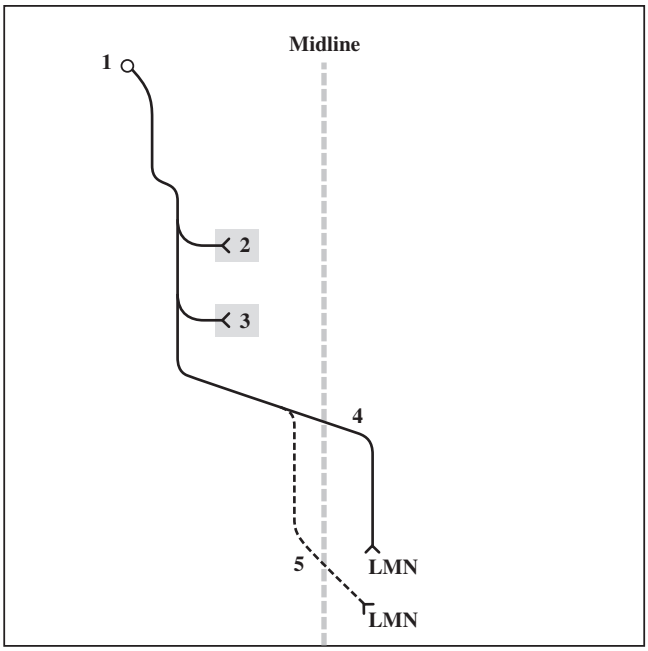


Figure 1.16. Schematic representation of the pyramidal motor system. Midline of the nervous system is represented by the dotted line. See text for complete description. (1) Pyramidal motor neuron with cell body (circle) in the motor cortex of the cerebrum. (2) Axons synapse at the level of the pons forming the corticopontine pathway. (3) Additional axons forming the corticonuclear tract synapse in the brainstem on the motor nuclei associated with various cranial nerves. (4) Additional axons decussate in the caudal brainstem and descend contralaterally into the spinal cord forming the lateral corticospinal tract to synapse on LMN (lower motor neurons) of the spinal nerves. (5) Remaining axons descend ipsilaterally through the brainstem and cross in the spinal cord at their site of synapse on LMN of the spinal nerves.

Figure 1.13. The LCS tracts impose upper motor regulation to the lower motor neurons in the spinal cord.

The remaining pyramidal fibers do not cross at the level of the pyramid in the myelencephalon. They descend ipsilaterally into the spinal cord forming the ventral corticospinal tract located in the white matter of the ventral funiculus. As the fibers of the ventral corticospinal tract reach the level of the spinal cord where they will synapse on the lower motor neurons, they cross to the opposite side prior to their synapse. Like their counterpart in the LCS tract, the ventral corticospinal fibers also provide a contralateral regulatory influence on the appropriate lower motor neurons of the spinal cord.

Extrapyramidal Motor Organization

The extrapyramidal motor system is so named because the nuclei and tracts contained within this division do not contribute to formation of the pyramids seen on the ventral surface of the myelencephalon. Anatomically, the extrapyramidal part of the motor system is composed of a myriad of nuclei and tracts located within all divisions of the brain. Whereas the pyramidal system provides regulation of the highly skilled motor activities, the extrapyramidal system provides regulation of coarse and stereotyped motor activities. In general, the extrapyramidal system provides regulatory influence on the lower motor neurons that are responsible for muscle tone and posture. A detailed explanation of the interconnections and functions of extrapyramidal centers and tracts is beyond the scope of this introductory overview of the nervous system. Therefore, only the major centers and tracts will be highlighted.

Extrapyramidal Centers of the Brain

The extrapyramidal motor system is of greater significance in animals than the pyramidal system. The extrapyramidal structures are widespread throughout the central nervous system and provide multiple polysynaptic pathways to ultimately regulate the activity of lower motor neurons. The cerebrum contains cortical and subcortical collections of extrapyramidal motor cells. Each of the four remaining adult divisions of the brainstem also have extrapyramidal nuclei.

Extrapyramidal motor neurons are scattered in the cortex of the cerebrum, with subcortical extrapyramidal nuclei also present. The corpus striatum is a collection of alternating white and gray matter structures located in the telencephalon as shown in Figure 1.17A. The gray matter of the corpus striatum is formed by the basal ganglia of the cerebrum. These ganglia, more correctly identified as basal nuclei, are the caudate nucleus, globus pallidus (also known as the pallidum), and the putamen. Within the processing network of the corpus striatum, generally speaking, the caudate nucleus and the putamen act as afferent centers that receive and process information. The globus pallidus acts as an efferent center to send information to other extrapyramidal centers. Nuclei in the rostral portion of the brainstem participate in the processing of information that is traveling through the extrapyramidal system. Examples of the diencephalic extrapyramidal nuclei are the zona incerta, endopeduncular nucleus, and subthalamic nucleus.

Within the mesencephalon, the major extrapyramidal nuclei are the red nucleus, the tegmental nucleus, and the substantia nigra. Of these three, the red nucleus is of particular importance. It gives rise to the rubrospinal tract that descends through the rest of the brainstem to reach the lower motor neurons of the spinal cord. The rubrospinal tract is localized in the lateral funiculus of the cord as shown in Figure 1.13. The rubrospinal tract is the principal motor tract in the extrapyramidal system in animals.

At the level of the metencephalon, a nuclear area of the reticular formation plays a role in extrapyramidal regulation. The pontine reticular nucleus sends axons contralaterally through the caudal portions of the brainstem to enter the spinal cord. These axons from the pontine, or ventral, reticulospinal tract shown in Figure 1.13. As these fibers pass through the ventral funiculus of the cord, they synapse on interneurons or lower motor neurons of the spinal cord to exert their regulatory control.

The medullary reticular nucleus is located in the reticular formation of the myelencephalon. It gives rise to descending axons that form the lateral reticulospinal tract. This tract descends contralaterally in the lateral funiculus of the spinal cord figure to synapse on interneurons or lower motor neurons (see Figure 1.13). Although the extrapyramidal motor system is characterized by numerous structures (Figure 1.17B), descending regulation reaches the lower motor neurons in the spinal cord mainly through three contralateral pathways, the

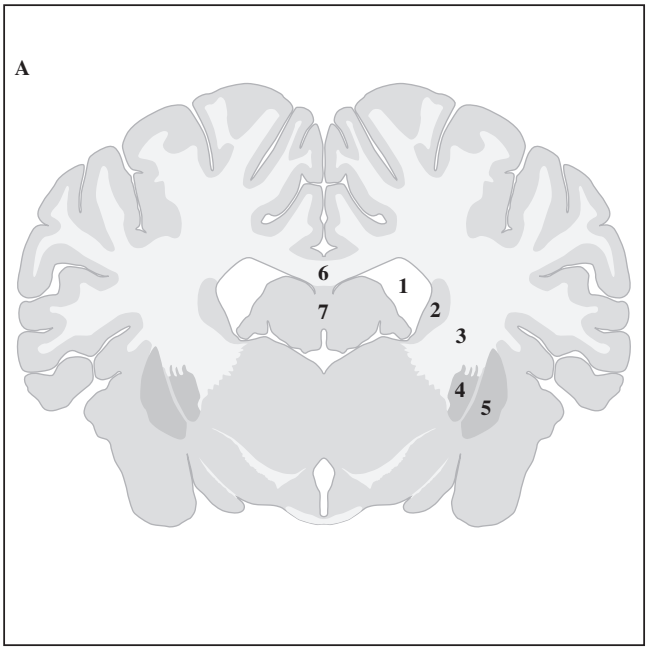


Figure 1.17A. Transverse section of the brain at the level of the mammillary body showing the corpus striatum. (1) Lateral ventricle; (2) Caudate nucleus; (3) Internal capsule; (4) Globus pallidus (pallidum); (5) Putamen; (6) Corpus callosum; (7) Hippocampus.

rubrospinal tract of the mesencephalon, the pontine reticulospinal tract of the metencephalon, and the medullary reticulospinal tract of the myelencephalon.

The tectospinal tract also transmits upper motor influence. This descending pathway shown in the ventral funiculus in Figure 1.13 originates in the tectum of the midbrain. Descending axons pass primarily to the cervical musculature to regulate cervical movements associated with visual reflex activity.

The remaining tract shown in Figure 1.13, the vestibulospinal tract, represents upper motor control that originates with sensory impulses detected by receptors in the vestibular system. The vestibular system is a special sensory system of the body that monitors position, rotation, and movement of the head. The purpose of the vestibular system is to adjust body posture in response to the changing impulses detected by the sensory receptors for balance and equilibrium located in the semicircular canals of the inner ear. Impulses travel in response to head movement along the vestibular portion of the vestibulocochlear nerve (CN VIII). The majority of the vestibular axons synapse in the brainstem on four pairs of vestibular nuclei. In turn, axons from the vestibular nuclei project to the cerebellum, the brainstem nuclei that regulate the extraocular eye muscles, and the spinal cord. Some of the vestibular fibers synapse in the flocculonodular lobe of the cerebellum. This phylogenetically older part of the cerebellum is responsible for providing the sensorimotor coordination necessary to maintain balance and equilibrium.

Ascending projections from the vestibular nuclei pass rostrally through the brainstem to the motor nuclei of the extraocular eye muscles as the ascending limb of the medial longitudinal fasciculus. Appropriate stimulation of the eye muscles in response to these vestibular impulses initiated by head movement produces conjugate eye movement.

The major fiber projection of the vestibular nuclei that enters the spinal cord forms the lateral vestibulospinal tract located in the ventrolateral funiculus of white matter as shown in Figure 1.13. A smaller projection travels through the spinal cord in the ventral funiculus adjacent to the ventral median fissure. This smaller bundle forms the medial vestibulospinal tract, also identified as the descending limb of the medial longitudinal fasciculus. The two vestibulospinal tracts are responsible for regulating the extensor muscle tone necessary to maintain balance and posture. Vestibulospinal tract adjustments help to coordinate the activity of the limbs and trunks in response to head movements detected through the vestibular receptors in the inner ear.

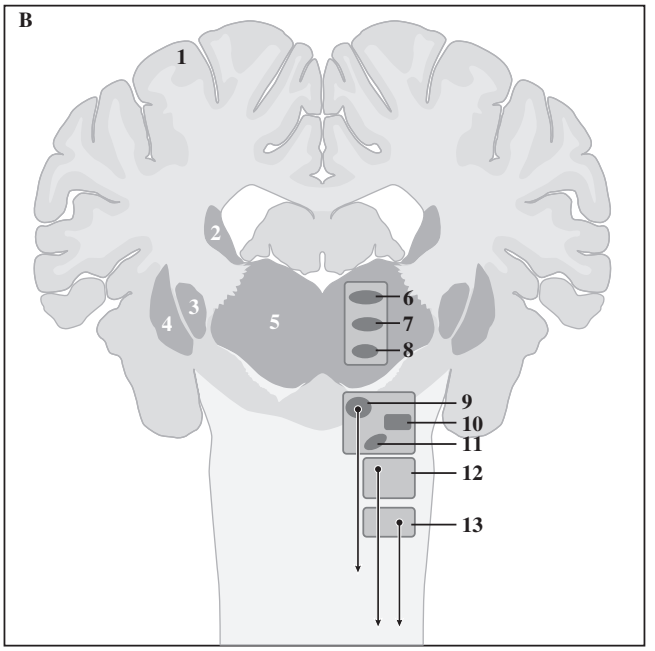


Figure 1.17B. Schematic topographic organization of extrapyramidal motor centers. Nuclei 6, 7, and 8 are in the diencephalon; 9, 10, 11 are in the mesencephalon; 12 is in the metencephalon; 13 is in the myelencephalon. (1) Cerebral cortex; (2) Caudate nucleus; (3) Globus pallidus (pallidum); (4) Putamen; (5) Diencephalon; (6) Zona incerta; (7) Endopeduncular nucleus; (8) Subthalamic nucleus; (9) Red nucleus; arrow represents rubrospinal tract that decussates and descends to spinal cord levels; (10) Tegmental nucleus; (11) Substantia nigra; (12) Pontine reticular nucleus; arrow represents pontine reticulospinal tract that decussates and descends to spinal cord levels; (13) Medullary reticular nucleus; arrow represents medullary reticulospinal tract that decussates and descends to spinal cord levels.

Neurologic Signs of UMN Dysfunction

A lesion that involves upper motor neuron structures or pathways essentially decreases or eliminates the regulatory control of the upper motor neuron on the lower motor neuron. As a result of the loss of this control, which is generally of an inhibitory nature on the lower motor neuron, a neurologic examination will reveal signs that are considered to be hallmarks of upper motor neuron disease: hypertonus, hyperreflexia, and spastic paralysis. Muscular atrophy that takes a relatively slow time to develop is also observed.

THE CEREBELLUM

The role of the cerebellum is to monitor sensorimotor information that travels through the nervous system. It acts to integrate this information to produce smooth, coordinated movement. The cerebellum is the superstructure attached to the brainstem at the level of the metencephalon by the cerebellar peduncles. It is separated from the cerebrum by an intervening space identified as the transverse cerebral fissure. The cerebellar peduncles are formed by various fiber tracts passing between the cerebellum and the brainstem. The naming convention to identify the cerebellar peduncles has been presented in the section on the metencephalon.

Topographic Anatomy of the Cerebellum

The cerebellar surface is divided into a midline strip, the vermis, and the tissue lateral to the vermis identified as the left and right cerebellar hemispheres.

The paravermal tissue can also be identified as the intermediate zone or the intermediate hemisphere as shown in Figure 1.18. The cerebellar surface is characterized by alternating grooves and ridges of tissue identified as the sulci and folia respectively. There is a close association of the phylogenetic development of the cerebellum with the grossly identifiable cerebellar lobes. The archicerebellum corresponds to the flocculonodular lobe on the ventral surface of the cerebellum. The paleocerebellum is represented by the rostral lobe. The neocerebellum corresponds to the caudal lobe and represents the highest level of cerebellar development as evidenced in mammals. As a general guideline, the primary fissure separates the rostral lobe of the cerebellum from the caudal lobe on the dorsal surface. On the ventral surface, the caudolateral fissure separates the caudal lobe of the cerebellum from the flocculonodular lobe.

Anatomic Organization of the Cerebellum

Figure 1.19A shows that the anatomic arrangement of the gray and white matter in the cerebellum is analogous to the arrangement that was seen in the cerebrum. Gray matter covers the cerebellar cortical surface that surrounds the deeper white matter. The cortical gray matter is divided into three layers. From superficial to deep, these layers are identified as the molecular, Purkinje, and granular layer. Subcortical gray matter is also present in the cerebellum where it appears as three pairs of cerebellar nuclei embedded in the white matter. From medial to lateral, these deep cerebellar nuclei are identified as the fastigial, interpositus, and dentate nuclei respectively (Figure 1.19B).

Functional Organization of the Cerebellum

While the cerebellum is a complex structure in terms of its role in the nervous system, a simplified overview can be presented to gain a fundamental understanding of cerebellar function. The cerebellum receives general proprioceptive information from the periphery along with information from both the pyramidal and extrapyramidal motor systems. Information about head position and movement (termed special proprioception) also enters the cerebellum.

The Purkinje cells in the cortex monitor and process all the incoming information. When activated as a result of the net summation of all the afferent impulses, the Purkinje cells send a normally inhibitory impulse to the appropriate cerebellar nuclei. The cerebellar nuclei in turn project to motor centers in the brainstem, which in turn project to the cerebral cortex to produce coordinated movement.

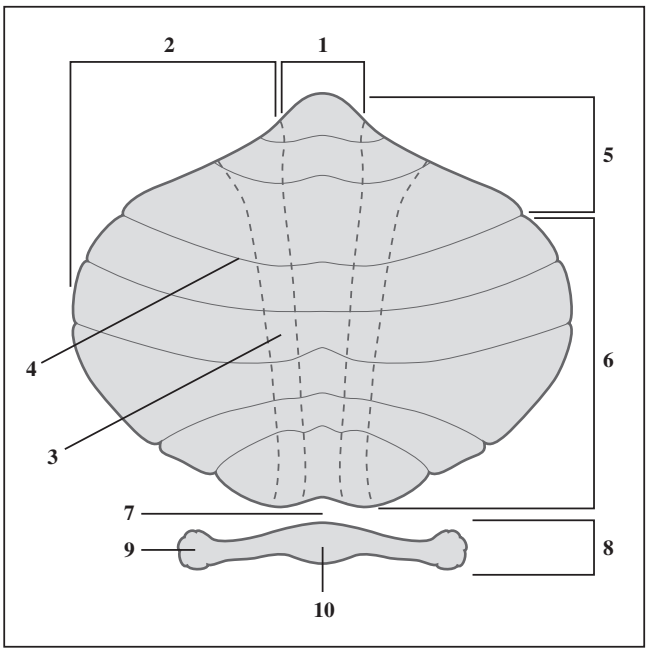


Figure 1.18. Schematic view of the cerebellum indicating anatomic regions. The cerebellum has been "unfolded" with the flocculonodular lobe positioned at the bottom of the diagram.
(1) Vermis
(2) Hemisphere
(3) Intermediate hemisphere
(4) Primary fissure
(5) Rostral lobe
(6) Caudal lobe
(7) Caudolateral fissure
(8) Flocculonodular lob
(9) Flocculus
(10) Nodulus

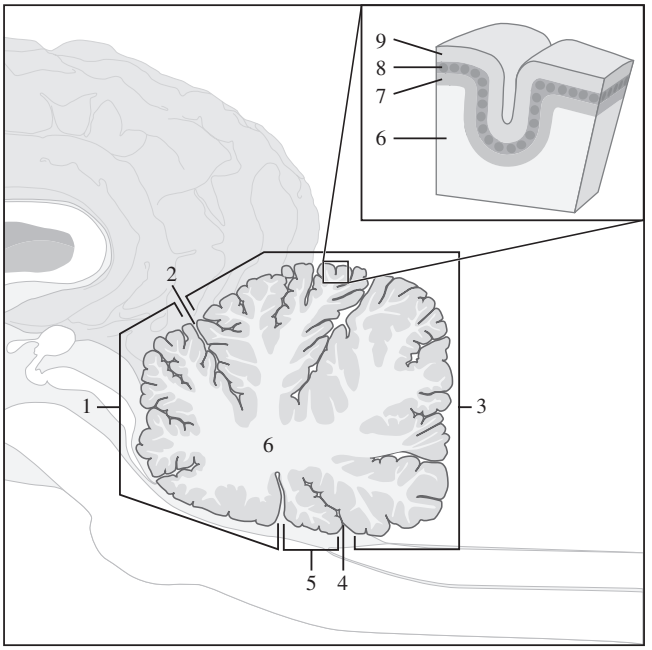


Figure 1.19A. Schematic view of the sagittally sectioned cerebellum. Inset shows cerebellar cortical layers. (1) Rostral lobe; (2) Primary fissure; (3) Caudal lobe; (4) Caudolateral fissure; (5) Flocculonodular lobe; (6) White matter (arbor vitae); (7) Granular layer; (8) Purkinje cell layer; (9) Molecular layer.

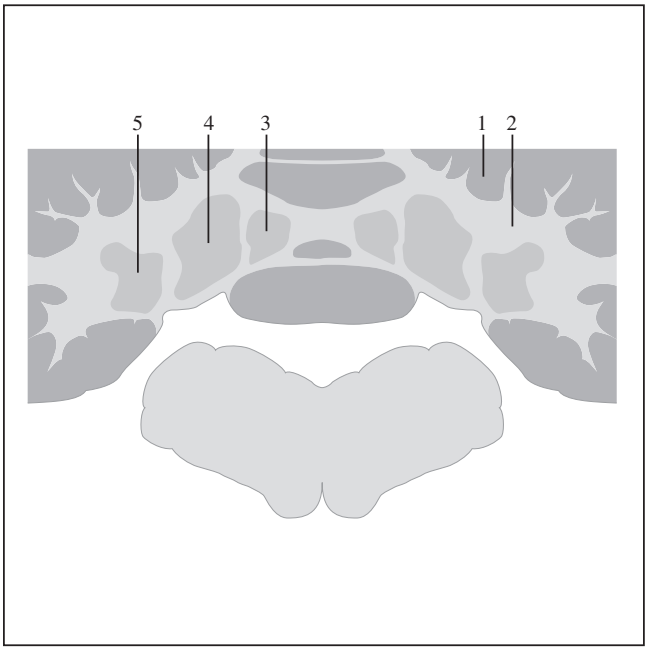


Figure 1.19B. Schematic view of transversely sectioned cerebellum dorsal to the brainstem. (1) Cerebellar gray matter; (2) Cerebellar white matter; (3) Fastigial nucleus; (4) Interpositus nucleus; (5) Dentate nucleus.

While there is some degree of overlap, it is possible to correlate functional areas of the cerebellar lobes with the type of movement that is regulated and coordinated. The archicerebellum corresponds anatomically with the flocculonodular lobe and maintains balance and equilibrium through the input of the vestibular system. The flocculonodular lobe also processes information that controls head and conjugate eye movements. This part of the cerebellum is identified as the vestibulocerebellum. The paleocerebellum has its functional area localized in the vermis and paravermal areas of the cerebellum. This area of the cerebellum coordinates activity for muscle tone and posture control. Because of these associations, this functional area is identified as the spinocerebellum. Finally, the neocerebellum has its functional equivalent in the hemispheres lateral to the intermediate zone. This area of the cerebellum coordinates voluntary and highly skilled movement. It is referred to as the pontocerebellum or cerebrocerebellum. Although this is a greatly simplified explanation of cerebellar connections, it is through these complex interactions that the cerebellum monitors motor, proprioceptive, and vestibular (balance) information to maintain muscle tone and equilibrium and produce smooth, coordinated movement. The signs of cerebellar disease can be related to the area of the cerebellum that has been affected and results in loss of its regulatory ability.

PERIPHERAL NERVES

Peripheral nerves transmit a mix of sensory and motor information. Sensory impulses are detected by numerous and varied nerve receptors in the periphery and are transmitted toward the central nervous system. Motor impulses originate in the CNS and travel through the peripheral nerves to provide motor innervation to somatic or visceral target structures of the body. This motor division of the peripheral system where nerve fibers leave the brainstem or spinal cord to reach their targets represents lower motor neuron innervation. Regulatory upper motor nerve fibers are confined within the CNS and are part of the central nervous system and therefore not part of the peripheral division. There are two broad categories of peripheral nerves, spinal nerves and cranial nerves. There is often confusion about the function of peripheral nerves, especially cranial nerves. This confusion can be dispelled with the realization that spinal and cranial nerves perform the same function of transmitting sensory and motor innervation that is passing between the CNS and peripheral structures. The distinction between spinal and cranial nerves therefore is not in function but in terms of their anatomic location. Put most simply, spinal nerves are so named because they are physically connected to the spinal cord; likewise, cranial nerves are so named because they are physically connected to the brainstem which is located in the cranium. Nerve fibers that enter the central nervous system transmit sensory impulses from the periphery. Nerve fibers that leave the central nervous system provide motor innervation to various targets throughout the body.

At the level of the spinal cord, each spinal nerve is attached to the cord by dorsal and ventral roots. The dorsal root of the spinal cord represents the equivalent of axonal processes that originated from sensory cell bodies located in the spinal ganglion, as shown in Figure 1.20. The ventral root is formed by axons that originated in large motor cells located in the ventral gray column and leave the spinal cord to innervate target structures in the periphery. The spinal nerve proper is a relatively short segment located at the level of the intervertebral foramen. At this level, the spinal nerve is composed of the intermingling of nerves of sensory nerve fibers from peripheral nerve receptors and the motor nerve fibers traveling to peripheral target structures. The spinal nerve divides into dorsal and ventral branches that carry sensory and motor impulses throughout the periphery.

Afferent Function of Peripheral Nerves

Spinal and cranial peripheral nerves will transmit afferent, or sensory, information from somatic and visceral structures. Impulses of pain, temperature, touch, position, and movement, i.e., nociception and proprioception, travel through the peripheral fibers of spinal nerves constituting a general somatic afferent system. Visceral receptors, as part of the general afferent system, detect sensory impulses that originate within body viscera related to temperature, blood pressure, gas and chemical concentrations, dilation, and movement of the body organs. For the spinal division of peripheral nerves, the sensory cell bodies are segmentally distributed and located in the spinal ganglia. Axons from these primary sensory cells generally synapse in the dorsal gray column. Information ascends to higher centers in the nervous system, or participate in local reflex activities.

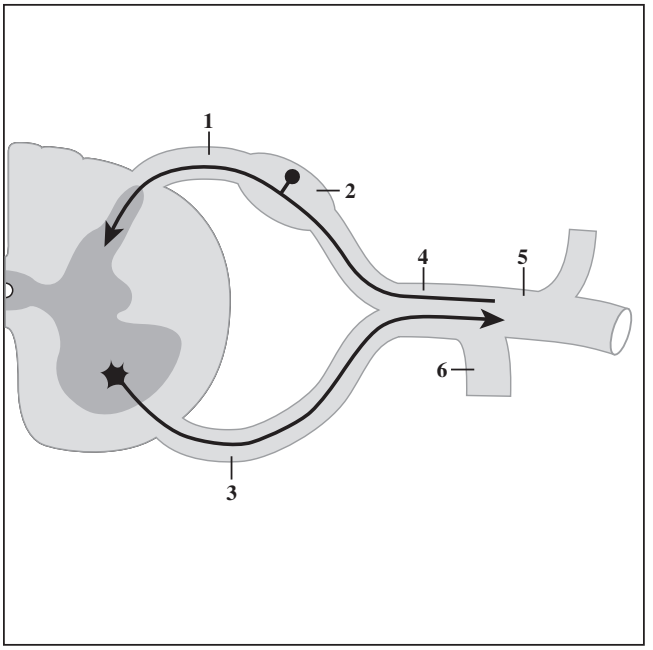


Figure 1.20. Spinal nerve anatomy. The dorsal root is formed by sensory neurons; the ventral root is formed by motor neurons. Arrowheads indicate sensory impulses travel toward the spinal cord and motor impulses travel toward the periphery. (1) Dorsal root; (2) Spinal ganglion (dorsal root ganglion); (3) Ventral root; (4) Spinal nerve proper; (5) Dorsal branch of the spinal nerve; (6) Ventral branch of the spinal nerve.

Not all cranial nerves participate in the transmission of sensory information from the periphery. Proprioceptive and nociceptive information from the head travel through the trigeminal nerve (CN V). This information is processed through a column of cells in the brainstem identified as the trigeminal sensory nucleus. Sensory afferents for balance and equilibrium travel through the vestibular portion of the vestibulocochlear nerve and synapse in the brainstem in the vestibular nuclei. The cochlear division of the vestibulocochlear nerve carries auditory afferents that synapse in the brainstem cochlear nuclei. Visceral afferent (via glossopharyngeal and vagus nerves) and taste fibers (via the facial nerve) synapse in another large sensory nucleus of the brainstem, the solitary nucleus. Afferent impulses for vision travel through the optic nerve (CN II) and synapse in the lateral geniculate nucleus of the diencephalon. Sensory afferent input for olfaction travels through the olfactory nerve (CN I) to synapse in the olfactory bulb of the rhinencephalon. These sensory cranial nerve nuclei are presented in Figure 1.21.

Efferent Function of Peripheral Nerves

Motor neurons are distributed along the length of the spinal cord in the ventral gray column. Motor fibers leave the spinal cord to travel through the spinal nerve to provide innervation to the skeletal muscles in the body. Motor innervation to the muscles of the head travel through various cranial nerves. Motor nerve fibers travel through select cranial nerves to provide autonomic innervation as previously described in the section on the autonomic nervous system.

The cranial nerves with motor function originate from nuclei scattered throughout the brainstem. The cells of the motor nuclei are arranged in three fragmented columns that can be functionally organized based on their target structures, as described below and shown in Figure 1.21.

Somatic Efferent Targets

The targets for this group of motor nuclei are the extraocular muscles and the muscles of the tongue. The efferent motor fibers to these targets originate in the oculomotor, trochlear, abducens, and hypoglossal nuclei.

Branchial Arch Targets

Skeletal muscle in this group originates from the branchial arches in the developing embryo. The

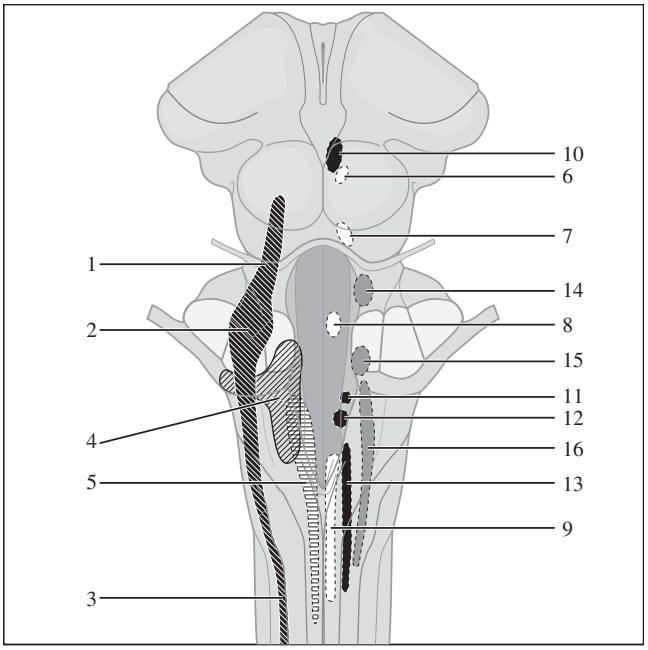


Figure 1.21. Schematic view of the dorsal brainstem. Sensory nuclei are indicated on the left, motor nuclei on the right. Motor nuclei with similar shading form functional groups for target structures as described in the text. (1) Mesencephalic nucleus of the trigeminal nerve; (2) Pontine sensory nucleus of the trigeminal nerve; (3) Spinal nucleus of the trigeminal nerve; (4) Vestibular and cochlear nuclei; (5) Solitary nucleus; (6) Oculomotor nucleus; (7) Trochlear nucleus; (8) Abducens nucleus; (9) Hypoglossal nucleus; (10) Edinger Westphal nucleus; (11) Rostral salivatory nucleus; (12) Caudal salivatory nucleus; (13) Dorsal nucleus of the vagus nerve; (14) Motor nucleus of the trigeminal nerve; (15) Motor nucleus of the facial nerve; (16) Nucleus ambiguus.

targets for this group are the muscles of mastication, the muscles of facial expression, and the muscles of the pharynx and larynx. The efferent motor fibers to these targets originate in the motor nuclei of the trigeminal and facial nerves, and the nucleus ambiguus which serves as the origin for the glossopharyngeal, vagus, and the internal root of the accessory nerve. The internal root of the accessory nerve gives rise to fibers that are distributed with the vagus nerve. The external root originating from cervical spinal cord levels innervates the brachiocephalicus, omotransversarius, trapezius, and strernocephalicus.

Autonomic System Targets

The target structures for this group are glandular tissue and cardiac and smooth muscle cells that receive parasympathetic motor innervation via the cranial nerves. The efferent motor fibers originate in the parasympathetic motor nuclei of cranial nerves 3, 7, 9, and 10. These parasympathetic nuclei are also identified by common names: Edinger–Westphal nucleus (CN III), rostral salivatory nucleus (CN VII), caudal salivatory nucleus (CN IX), and the dorsal motor nucleus of the vagus (CN X). A summary of cranial nerve function is found in Table 1.3.

Table 1.3. Functional Classification of the Cranial Nerves

Cranial Nerve	Number	Function
Sensory		
Olfactory	CN I	Olfaction
Optic	CN II	Vision
Vestibulocochlear	CN VIII	Balance and hearing
Motor		
Oculomotor Parasympathetic to eye	CN III	Extraocular eye muscles
Trochlear	CN IV	Extraocular eye muscles
Abducens	CN VI	Extraocular eye muscles
Accessory	CN XI	Pharyngeal and laryngeal muscles; cervical muscles
Hypoglossal	CN XII	Lingual muscles
Mixed		
Trigeminal	CN V	General sensation to face; motor to muscles of mastication
Facial	CN VII	Taste sensation; motor to muscles of facial expression; parasympathetic for salivation and lacrimation
Glossopharyngeal	CN IX	Pharyngeal sensation; taste; swallowing muscles; parasympathetic for salivation
Vagus	CN X	Sensation pharynx and larynx; swallowing; parasympathetic for thoracic and abdominal organs

2
Cerebrospinal Fluid and the Blood–Brain Barrier

Martin Furr and Frank Andrews

Cerebrospinal fluid (CSF) is a clear, colorless fluid that fills the brain ventricular system, central canal of the spinal cord, and subarachnoid space. It penetrates and bathes all central nervous system (CNS) tissue and is contiguous with the CNS extracellular fluid.[1] The CSF is an ultrafiltrate of plasma, with all the constituents of plasma but with differing concentrations and relative proportions.

FORMATION

The CSF is produced as an ultrafiltrate of plasma and is actively secreted by ependymal cells and choroid plexus. While the majority of CSF is produced by the choroid plexus in the lateral ventricles, approximately 30–40% of CSF may be produced by the ependymal lining of the ventricles, the leptomeninges, and brain and spinal cord blood vessels.[1] Production is directly proportional to the transport of sodium via a Na-K ATPase in the brush border of the choroidal epithelium and is independent of vascular hydrostatic pressure. The CSF is formed at a constant rate, which in humans ranges from 0.32 to 0.37 ml/min.[2,3] The rate varies with species and has been estimated to be 0.2–0.5 ml/min/g of choroid plexus tissue.[4] The rate of formation of CSF in the horse has not been determined.

The rate of CSF production can be altered by a variety of compounds. Carbonic anhydrase and Na-K ATPase inhibitors and hyperosmolality decrease production rate, while cholera toxin and adrenergic stimulation increase CSF production rate.[4] Osmotic agents and hypertonic solutions such as mannitol and dimethyl sulfoxide, when given intravenously, decrease CSF production in other species, but the effects of these compounds on the production of CSF in the horse have not been investigated.

Following formation, CSF flows into the third and fourth ventricles, over the cerebral hemispheres, then exits caudally through foramina in the fourth ventricle to enter the subarachnoid space. Pulsation of blood in the choroid plexus forces the CSF in a cranial to caudal flow, and CSF is absorbed by collections of arachnoid villi in the dural sinuses or the cerebral veins. When CSF pressure exceeds venous pressure, these villi act as a one-way ball valve forcing CSF flow to the venous sinus.

The CSF functions to protect the brain from trauma and to maintain a consistent extracellular environment for the CNS. The CSF provides physical support (i.e., buoyancy) and cushioning of the CNS as a result of its specific gravity (1.004–1.006) and fluid pressure, which effectively reduces the weight of the brain 30-fold.[4] It also serves as a physiologic medium to transport a variety of compounds (neurotransmitters) and to regulate the chemical environment of the CNS ("sink-action"). Because the CSF bathes the entire CNS, diseases of the brain and spinal cord may result in changes in its composition, which can be used as a diagnostic aid.

BLOOD–BRAIN BARRIER

The blood–brain barrier (BBB) and blood–CSF barrier separate brain interstitial fluid and CSF from the general circulation, respectively. These structures were once thought to be the same, but extensive research has shown that the BBB and blood–CSF barriers are two independent membrane barriers with separate functions.[5] The BBB has a large surface

area and separates the brain interstitial fluid from the general circulation. The blood–CSF barrier has approximately 5000-fold less surface area and is made up of the choroid plexus and other tiny regions of the ventricles.[6] The composition of brain interstitial fluid is determined by active transport of substances through the BBB, whereas the composition of the CSF is determined by the secretory processes through choroid plexus epithelia. Because these two barriers are functionally separate, their anatomic compositions differ significantly. This may be the reason why extensive damage to brain parenchyma may result in minimal to no changes in CSF composition. The blood–CSF barrier separates the CSF from the general circulation and is the basis for the unique characteristics of this fluid. The BBB and blood–CSF barriers are found in almost all regions of the CNS and have unique anatomic characteristics. The BBB is composed of capillary endothelial cells, basal lamina, pericytes, astroglia, and perivascular macrophages, while the blood–CSF barrier is composed of capillary endothelium, loose connective tissue, basal lamina, and ependymal cells. Certain (small) areas of the CNS do not have a BBB, including portions of the hypothalamus, area prostrema, and subfornical and subcommissural regions.[7] This observation has not been confirmed in horses; however, it is anticipated to be similar to other mammalian species. Damage to the blood–CSF barrier can lead to alterations in CSF composition, and thus analysis of CSF can indicate damage (Figure 2.1).

The integrity of the BBB can be evaluated by use of the albumin quotient (AQ).[8] In normalcy, CSF albumin concentrations vary in direct proportion to the serum albumin concentration. This relationship is expressed mathematically as:

$$AQ = \frac{Albumin_{csf}}{Albumin_{serum}} \times 100$$

Iatrogenic blood contamination of the CSF samples, intrathecal hemorrhage, or inflammation/traumatic disruption of the BBB will result in an elevated AQ. A normal AQ value of <2.1 for adults and 1.8 ± 0.2 for foals is reported.[8]

INDICATIONS FOR CSF ASSAY

Analysis of CSF is a useful adjunct in the evaluation and diagnosis of neurologic disease in horses. Ideally, CSF collection and evaluation should be performed on any horse demonstrating undiagnosed neurologic abnormalities. In addition, CSF evaluation should be considered in horses with fever of unknown origin, as meningitis is an uncommon cause of fever in horses. It must be remembered, however, that it is not uncommon for the CSF composition to be normal even in horses with obvious neurologic disease. Several possible explanations for this exist including timing of the collection in relation to the clinical signs and pathologic changes, extradural or ventral root neuropathies, and sampling too far from the site of the lesion. Collection of CSF may occur early in disease before organic changes in the CSF occur, or late in the disease after the organic changes have resolved.

Extradural lesions also do not result in changes in CSF parameters and include compressive lesions (cervical stenotic myelopathy, synovial cysts, and extradural tumors), peripheral neuropathies such as botulism and tetanus, and metabolic diseases. Furthermore, sampling too far from the site of the lesion may result in normal CSF results, such as failure to detect hemorrhage in the case of acute brain trauma if a sample is taken from the lumbosacral (LS) space acutely. Also, since CSF flows in a caudal direction, CSF collected rostral to a focal lesion may be normal.

On the other hand, inflammatory disease, or conditions that result in tissue necrosis, causes significant changes in the CSF. The observation that the CSF may be normal should not be considered as justification to forego spinal fluid collection, since normal CSF parameters have value in ruling out some diseases. Furthermore, it is not possible to predict in which clinical patient the CSF parameters will be of value or not; thus collection should be considered in all horses exhibiting neurologic disease.

Rarely are changes in CSF confirmatory of a specific diagnosis, rather they allow individual diseases to be grouped together into categories, such as acute and chronic inflammation, degeneration, and vasculitis. This allows the clinician to narrow the list of possible diagnoses to those that are known to produce changes which are consistent with the observed changes in the patient sample. The presence of bacteria, fungi, or neoplastic cells would be confirmatory evidence of a specific diagnosis.

CSF COLLECTION

The technique of atlanto-occipital (AO) CSF collection has been previously described. The technique is

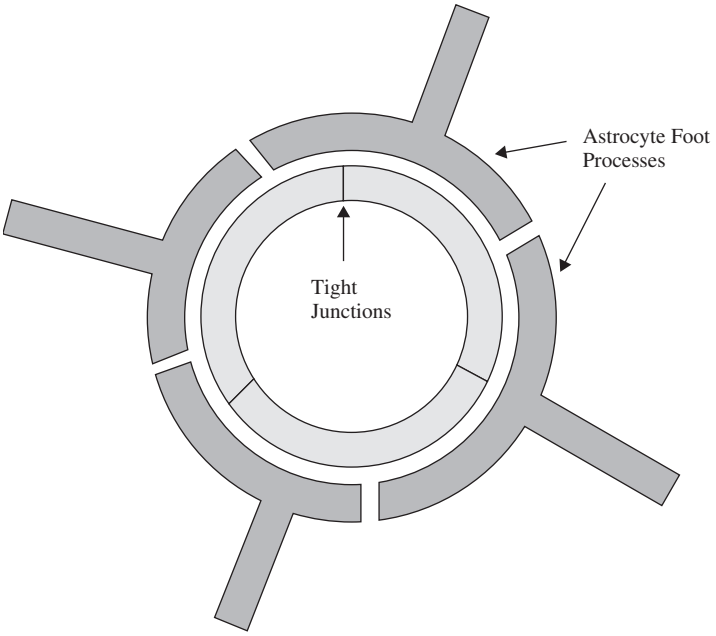


Figure 2.1. Schematic diagram showing the principal relationships that establish the blood–brain barrier. The inner ring is the endothelial cell layer with tight junctions, and the outer ring demonstrates the close approximation of the astrocyte foot processes.

simple; however it does require that the horse be anesthetized. This may or may not be advisable in all cases, and the benefits of collecting the fluid versus the risks of general anesthesia must be considered on a case-by-case basis. In most cases, an AO CSF sample can be collected quickly following short-acting injectable anesthesia.

After the horse is anesthetized, the poll is clipped and aseptically prepared, and the horse's head is flexed to expand the AO space. An 18-gauge, 3.5-inch spinal needle is inserted at the point at which a line drawn between the cranial borders of the atlas intersect midline. The needle is directed toward the lower jaw and advanced until the dura is penetrated, usually at a depth of about 2–2.5 inches (5 cm) in the mature adult horse. It is important to ensure that the needle is advanced in the median plane, as it is possible to miss laterally if the needle is angled. Resistance to advancing the needle will increase as the needle penetrates the nuchal ligament, then will abruptly decrease, resulting in a characteristic "pop". The pop is more noticeable at the AO space than the LS, and needle advancement should cease immediately once it is felt. The stylet can then be withdrawn and fluid collected. The fluid should flow freely without the need for aspiration in most cases. If no fluid is present, the stylet should be replaced and the needle advanced in 1-mm steps, attempting collection between each step. Relatively large volumes of CSF (up to 90 ml) can be withdrawn from an adult horse, but usually 5–10 ml is adequate for analysis. In neonates, it is prudent to withdraw only 1–2 ml to minimize the risk of tentorial herniation.

The ultrasonic anatomy of the AO joint and space of the horse has been described, and a method for ultrasound-guided AO puncture is described.[9,10] While it is demonstrated that the AO puncture can be performed under ultrasound guidance, it is rarely if ever necessary, and this approach has not been shown to have any particular advantages.

Follow-up care after an AO CSF collection is minimal. Non-steroidal anti-inflammatory drugs can be given if there is neck soreness. It is advisable to keep the horse in a stall and feed them hay from a haynet or elevated rack for 1–2 days after the tap. This prevents the horse from putting its head down to graze, which appears to increase the degree of neck soreness following an AO puncture.

The technique of CSF collection from the LS space is also well described in the literature. Horses can be restrained in a set of stocks (as is the authors preference), or restrained in the open. Stocks are

advisable as they provide a degree of protection from reflexive kicks during the procedure. A nose twitch is applied and the horse sedated. Combinations of xylazine (250 mg IV) and butorphanol (5 mg IV) for the 450-kg horse provide a good degree of sedation with a minimum degree of unsteadiness. Alternatively, detomidine (5–10 mg IV) can be used. The optimum site is the point on midline up to 1 cm cranial, to the point which is intersected by a line drawn between the cranial borders of the tuber sacrale (Figure 2.2). This is routinely determined by visual examination and palpation of the landmarks. The ultrasonic anatomy of the site has been described, however, and ultrasound examination for landmarks may be beneficial for those horses which are obese and in which the landmarks are difficult to palpate. When using ultrasound guidance, the insertion site is on midline 0.5 to 1 cm cranial to the point at which the tuber sacrale are most superficial.[11] The site should be clipped and scrubbed, and the subcutaneous tissue infiltrated with local anesthetic. Following this, a small stab incision can be made with a #15 blade—this is advisable as it minimizes dulling of the spinal needle. A 6- to 8-inch, 18-gauge spinal needle is then inserted and stabilized at the skin surface using one hand and the needle advanced with the opposite hand. The needle should be advanced steadily, not with jerking movements, and the operator must ensure that the needle is advanced straight down, without lateral or cranial–caudal deviations. It is sometimes useful to have an assistant stand well behind the horse and ensure that the needle is advancing perpendicularly to the horse's back. If not, the needle should be withdrawn almost to the surface and re-directed. If it is not withdrawn to the surface, the needle will follow the previous needle path. The LS space will be encountered at a depth of about 6 inches (13 cm) in most average-sized horses. As the needle approaches the space, increasing resistance will be felt, then the resistance will abruptly decrease as the needle penetrates the ligamentum flavum. This is felt by the operator as a "pop" and is usually a good indication that the membranes have been penetrated and the needle is well positioned. Penetration of the membranes is often accompanied by a reaction from the horse, which may vary from no reaction at all, restlessness, a tail flick, stomping of the foot, or tightening of the caudal muscles. Occasionally, a very violent reaction can be seen; however with proper sedation and a sharp spinal needle, these reactions are thankfully rare. Persons restraining the horse should be made aware that these are possible, however.

Once the dura has been penetrated, the stylet can be removed and CSF may be collected by gentle aspiration using a 5- or 10-ml syringe. It is important to avoid placing strong negative pressure on the syringe, as this can lead to blood contamination of the subsequent sample, or plugging of the needle with tissue. If negative pressure is felt, the stylet should be replaced, the needle advanced, and collection attempted again.

If no fluid can be retrieved, and the operator has confidence that the needle is properly placed, then the needle can be advanced by 1 mm at a time, with fluid collection attempted again until fluid is recovered. Alternatively, the needle can be rotated 90 degrees, with collection attempts repeated. Also, the horse's head can be raised and held up for a few minutes, and both jugular veins can be occluded (Queckenstedt maneuver) to increase intracranial pressure (ICP) and promote CSF movement caudally.

If the needle contacts the bone without feeling the characteristic "pop," or at a depth less than expected, the needle should be removed and redirected cranially or caudally until a proper needle depth is achieved or the space is penetrated (Figure 2.3).

When the sample is collected, the CSF should be withdrawn slowly with gentle aspiration. Iatrogenic blood contamination of the sample, rather than hemorrhage, is suggested if the blood is nonhomogenously distributed in the sample. That is, typically a small "stream" of blood can be seen rising in the syringe, then swirling to mix with the sample. In samples collected from horses with CNS hemorrhage, the blood is typically homogenously distributed and does not clear after multiple syringes have been removed (the "three tube test"). If the blood contamination remains uniform throughout the sample, it is most likely truly representative of the CSF. If gross blood is recovered, the needle should be discarded and a fresh needle used for a second attempt. Clear fluid can be recovered in these circumstances, although not in all cases. It should be recognized also that it may not be possible to enter the LS space in some animals due to calcification of the ligaments, for example.

Aftercare for horses following an LS spinal tap is minimal. The site should be kept clean and dry and observed for swelling or discharge. Phenylbutazone





Figure 2.2. The large dots demonstrate the palpable landmarks for the lumbosacral collection site and their corresponding anatomic sites. The dorsal spine at the arrow is not externally palpable in most horses, unless they are exceedingly thin. The insertion point for the needle is shown by the square marker.

or similar analgesics are rarely necessary but may be useful if multiple attempts were needed to get the sample.

A technique has been described for accessing the cerebral ventricles of the horse via a trephination site through the frontal bone. The procedure was easily performed in anesthetized horses and has utility in physiological experimentation in the horse.[12]

As in most procedures, complications may occur in a small percentage of individuals. Complications that may result from CSF collection include introduction of infectious agents into the CNS (septic meningitis), aseptic meningitis from hemorrhage, pain and swelling at the site of needle entry, or trauma associated with recovery from anesthesia. The author has occasionally seen horses flip over backward or fall during or following standing LS CSF tap. This usually occurs when the horse reacts badly or is severely ataxic during collection. Additional complications that may occur when collecting CSF from the AO space include spinal cord penetration ("pithing") if the needle is advanced too deeply, herniation of the cerebellum, and fractures or worsening of neurologic signs after anesthetic recovery. Complication rates have not been reported following CSF collection in horses but are widely believed to be very low.

CEREBROSPINAL FLUID

Pressure

The production of CSF within the fixed-volume compartment of the nervous system leads to a fluid pressure within the CNS. This ICP can be determined by a variety of techniques. Monitoring of ICP has been found to have both prognostic and therapeutic benefits in human patients with a variety of disorders, including head trauma, subdural hematoma, and brain edema. The two major factors that determine ICP are the arterial pressure and the intracranial venous pressure. There are three

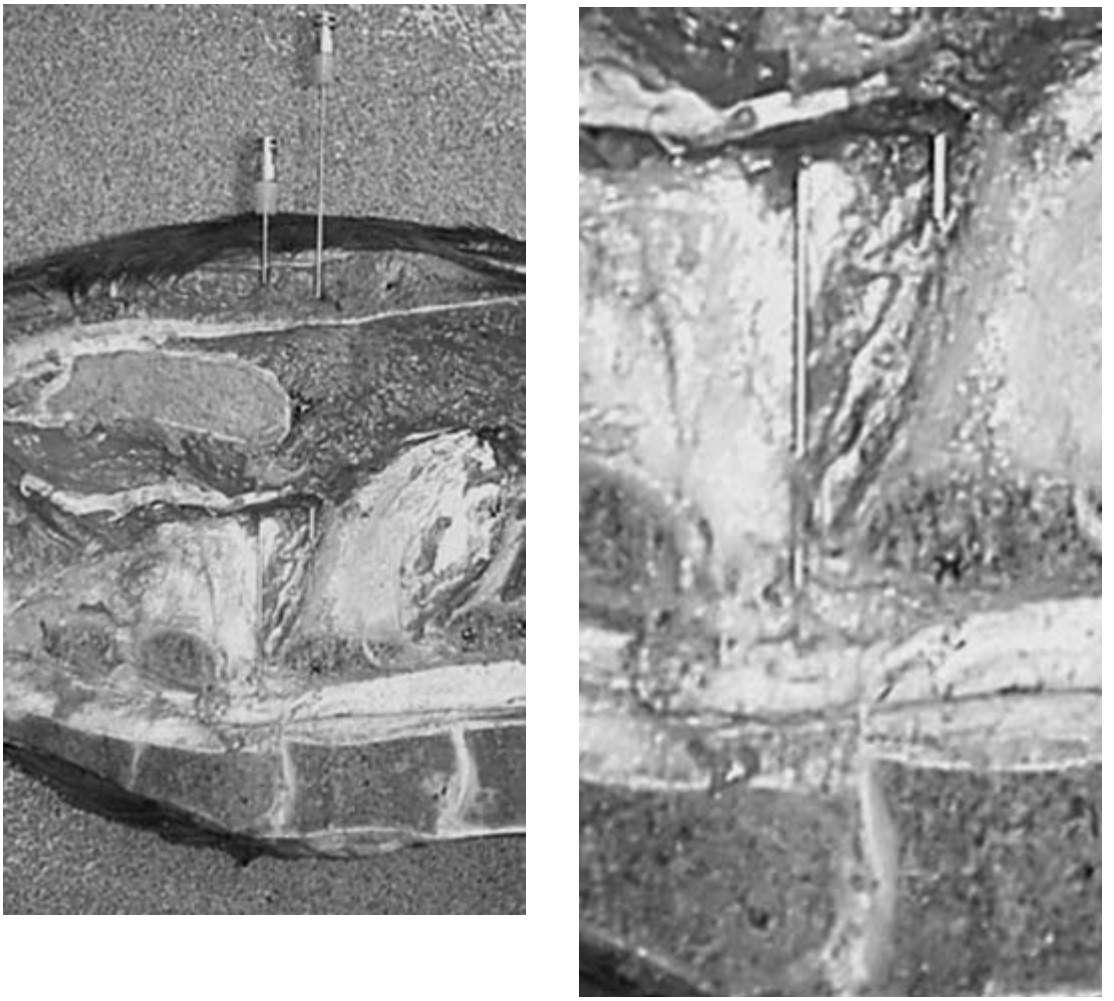


Figure 2.3. This sagittal section demonstrates the position of the needle for a correct lumbosacral fluid collection. The needle to the right in panel a is placed too far cranially and is contacting bone at too shallow a depth, resulting in more needle exposed. When performing a lumbosacral fluid collection, this observation would suggest redirecting the needle until bone is contacted at a greater depth.

components of the CNS that interact to generate ICP: brain, blood vascular component, and CSF. In accordance with the Monro–Kellie doctrine, an increase in the volume of one component must be compensated for by a decrease in the volume of at least one of the other components, or an increase in pressure. Therefore, venous distention, associated with venous obstruction or increased central venous pressure, results in increased ICP. By this mechanism, occlusion of the external jugular veins will result in an increased ICP—this is the foundation of "Queckenstedt's test" for spinal occlusion. In this test, jugular occlusion should lead to an increase in the CSF pressure measured at the lumbar space. If this does not occur, then spinal subarachnoid blockage must exist. The Queckenstedt maneuver can be used as an aid during spinal fluid collection, as described above.

The normal ICP for horses has been reported in only limited fashion. Using manometric techniques, the "opening pressure," that is the pressure obtained before removal of any fluid, is reported to be 150–500 mm H_2O (11.5–38.5 mm Hg) in the AO space, with a mean value of 308.8 mm H_2O (23.7 mm Hg).[13] The AO CSF closing pressure, that is the pressure after removal of a sample of CSF, was reported to be 75–400 mm H_2O (5.8–30.8 mm Hg) with a mean value of 223.5 mm H_2O (17.2 mm Hg).[13] Lateral ventricle CSF pressure is similar to AO pressure and has been reported as 19.7 ± 2.4 mm Hg in anesthetized normal adult horses in lateral recumbency.[14] Head position has a profound effect upon CSF pressure, and in awake standing horses ICP was only 2 ± 4 mm Hg.[15] Lumbosacral CSF pressures are highly correlated to lateral ventricle CSF pressure ($r^2 = 0.94$), but specific values were not reported.[14] These authors did not detect a change in CSF pressure following the use of xylazine, but hypercapnia did increase CSF pressure markedly when the $PaCO_2$ increased to 80 mm Hg.[14] Using a subdural catheter and fluid-coupled transducer system, the ICP in a group of neonatal foals ranged from 5.8 to 9.5 mm Hg over the first 3 days of life.[16]

Table 2.1. Turbidity Scale for Evaluation of Cerebrospinal Fluid

Turbidity Score	Description of Appearance
0	Crystal clear
+1	Turbidity barely visible; faintly hazy or cloudy
+2	Turbidity clearly present; newsprint easily readable through sample
+3	Turbidity obvious; newsprint not easily readable through sample
+4	Almost opaque; newsprint not readable through sample

Composition

In normalcy, the CSF is clear and colorless with a viscosity similar to water. The CSF sample (minimum of 1 ml) should be examined for clarity and appearance in a clean, clear glass tube. A similar volume of clean water can be used for side-by-side comparison. Slight turbidity of the CSF will be noted at a cell count of above 400 cells/mm^3.[17] Tyndall's effect is described as a "snowy" or "sparkling" appearance when the fluid is observed and mildly agitated in direct sunlight. This appearance will be observed at cell counts below 400 cells/mm^3. Turbidity is typically scored on a scale from 0 to 4+, with 0 being normal and 4+ being so turbid that newsprint cannot be read through the tube. Occasional small bits of epidural fat can be seen and are not considered significant (Table 2.1).

Xanthochromia, a yellowish or occasionally yellow-orange discoloration of the fluid, arises due to the presence of bilirubin.[17] Most commonly, this occurs following rupture of red blood cells (RBCs) in the CSF, but may occur due to hyperbilirubinemia. RBC lysis with development of xanthochromia takes 1–4 h after the hemorrhagic event.[18] In humans, this discoloration may persist for up to 2–4 weeks after an extensive bleed. High total protein (over 150 mg/dl) may also cause a mild xanthochromia.[18] In neonatal foals, the fluid may be slightly xanthochromic in foals up to 10 days of age.[19] Any xanthochromia greater than mild is considered abnormal, however (Table 2.2).

The cellular composition of CSF in both adult horses and foals has been reported.[13,19,20] In normalcy, the CSF cell count is very low, with clinical reference values for white blood cells being 0–6 cells/μl for both adults and foals. Leukocytes are almost totally mononuclear cells, and neutrophils and eosinophils are almost never seen in normal horses and should be regarded with suspicion, even if the total cell count is low. Owing to the low concentration of protein, cells within the CSF deteriorate rapidly; hence analysis should ideally occur within 1 h of collection. If the analysis of the CSF will be delayed, the sample should be split and one portion mixed with an equal volume of 40% ethanol until analysis.

Differential cell counts should be performed and require concentration methods due to the usually low number of cells in CSF. The sample can be filtered through a Millipore filter, or ideally prepared in a cytocentrifuge, then stained. Neutrophilic pleocytosis occurs in horses with infectious (bacterial or mycotic meningitis, Eastern equine encephalitis [EEE], Western equine encephalitis [WEE], and Venezuelan equine encephalitis [VEE]) or inflammatory conditions (trauma or chemical meningitis from hemorrhage or injection of ionic or

Table 2.2. Reference Values for Adult Equine Cerebrospinal Fluid

Parameter	Atlanto-occipital	Lumbosacral
Specific gravity[14]	1.004–1.008	1.004–1.008
Leukocytes (cells/ml)[10]	0–7	0–7
Erythrocytes (cells/ml)	Less than 50	Less than 50
Total protein (mg/dl)	10–120[10]	10–120[10]
Immunoglobulin G (mg/dl)[8]	3.0–8.0	3.0–10.5
Albumin quotient[8]	1.0–2.1	0.9–2.4
Glucose (mg/dl)[10]	30–70% of plasma value	30–70% of plasma value
Lactic acid (mg/dl)	1.92 + 0.12	2.3 + 0.21
Sodium (mEq/L)[10]	140–150	140–150
Potassium (mEq/L)[10]	2.5–3.5	2.5–3.5
Chloride (mEq/L)[10]	95–123	95–123
Calcium (mg/dl)[10]	2.5–6.0	2.5–6.0
Phosphorus (mg/dl)[10]	0.5–1.5	0.5–1.5
Urea nitrogen (mg/dl)[10]	5–20	5–20
Creatine kinase (IU)[10]	0–8	0–8
Lactate dehydrogenase (IU)[10]	0–8	0–8
Aspartate transferase (Sigma-Frankel units)[10]	15–50	15–50

nonionic contrast agents during a myelographic study) of the CNS. CSF lymphocytic pleocytosis is relatively uncommon in horses with nervous system disease.[18] Increased CSF lymphocyte counts may be seen in horses with CNS lymphoma, viral meningitis, specifically West Nile virus encephalitis, and equine protozoal myeloencephalitis (EPM). CSF eosinophilic pleocytosis is rare but has been reported in horses with verminous encephalitis due to *Halicocephalobus* sp.[21]

In normalcy, the CSF does not contain circulating RBCs, but they are commonly observed in CSF samples due to iatrogenic hemorrhage. CSF RBC concentrations up to 2000 cells/μl have been reported as normal by one author, although the mean number of CSF RBCs in this report was 195 cells/μl.[13] Higher numbers most likely reflect contamination from trauma during collection. The acceptable quantity of RBCs in CSF has decreased substantially in recent years and is considered to be a value of less than 50 RBC/ml by one author.[22]

Interpretation of a CSF sample which contains blood is particularly challenging as it is difficult to determine whether the elevated cell counts (both RBC and WBC) in the CSF are due to hemorrhage or simply from iatrogenic hemorrhage during collection. Horses with severe inflammatory disease and/or infections often have some component of blood in the CSF. Assuming that this is iatrogenic might lead to incorrect interpretation of the sample. To minimize the chances for this error, correction formulas have been proposed for both total protein and WBC count. Proposed formulas are:

$$\mathrm{WBC}_{\mathrm{added}} = \frac{\mathrm{WBC}_{\mathrm{blood}} \times \mathrm{RBC}_{\mathrm{csf}}}{\mathrm{RBC}_{\mathrm{blood}}}$$

$$\mathrm{Protein}_{\mathrm{added}}\,(\mathrm{mg/dl}) = \mathrm{Serum\ protein}\,(\mathrm{mg/dl}) \times (100 - \mathrm{PCV}) \times \frac{\mathrm{RBC}_{\mathrm{csf}}}{\mathrm{RBC}_{\mathrm{blood}}}$$

In these calculations, "$\mathrm{WBC}_{\mathrm{added}}$" and "$\mathrm{protein}_{\mathrm{added}}$" refers to the number of WBCs or amount of total protein added to the fluid as a result of the blood contamination. A useful approximation of the white blood cell count can also be obtained in the following manner. Assuming a normal hemogram, 1 WBC/mm^3 for every 700 RBCs in the CSF is subtracted from the total $\mathrm{CSF}_{\mathrm{wbc}}$. From this, if a CSF sample has a RBC count of 7000 and 100 WBC/μl, then 10 WBCs could

be accounted for by the added blood.[17] The CSF prior to blood contamination would then have a corrected, or "true" WBC count of 90 cells/μl. The results of such correction procedures should be interpreted with caution,[23] as one author who evaluated similar (but not precisely the same) equations for equine CSF reported them not to be accurate.[24] In the authors' opinion, it appears that blood contamination only minimally increases the CSF WBC count, and this effect can almost be discounted unless the amount of blood is large. However, blood contamination has a profound effect upon CSF protein and immunoassay results (Table 2.3).

Plasma proteins gain access to the CSF primarily by diffusion across the blood–CSF barrier. This diffusion is determined by the radius of the protein molecule which is directly related to the molecular weight.[25] Most of the blood proteins are represented in the CSF; however the relative proportions of each are altered as a reflection of the filtering function of the BBB. Normal CSF total protein concentration is roughly 1/100th that of the blood plasma.

Table 2.3. Reference Ranges for Equine Neonatal Cerebrospinal Fluid

Parameter	Atlanto-occipital	Lumbosacral
Leukocytes (cells/ml)	<5[15]	0.87 ± 1.3[40]
	1.3 ± 1.2 (AO site)[40]	
Erythrocytes (cells/ml)	46 ± 85 (range 0–317)[15]	239 ± 349[40]
	208 ± 471[40]	
Total protein (mg/dl)[15]		83.6 ± 16.1[40]
<48 h old	109 ± 9.7[15]	
11–14 days old	81.0 ± 22.8[15]	
21–22 days old	60.5 ± 22.4[15]	
31–42 days old	58.5 ± 17.0[15]	
7 days old	82.8 ± 19.2[40]	
Immunoglobulin G (mg/dl)[40]	10.2 ± 5.5	9.9 ± 5.7
Albumin quotient[40]	1.86 ± 0.29	1.85 ± 0.51
IgG index[40]	0.519 ± 0.284	0.482 ± 0.270
Glucose (mg/dl)[15]		Not reported
<48 h old	98.8 ± 12.0	
11–14 days old	67.3 ± 12.0	
21–22 days old	65.3 ± 4.5	
31–42 days old	70.0 ± 5.4	
Sodium (mmol/l)[15]		Not reported
<48 h old	148.0 ± 7.2	
11–14 days old	152.2 ± 1.2	
21–22 days old	153.8 ± 2.5	
31–42 days old	151.7 ± 1.5	
Potassium (mmol/l)[15]		Not reported
<48 h old	3.01 ± 0.17	
11–14 days old	3.60 ± 1.12	
21–22 days old	3.06 ± 0.08	
31–42 days old	2.96 ± 0.07	
Magnesium (mg/dl)[15]		Not reported
<48 h old	2.43 ± 0.16	
11–14 days old	2.51 ± 0.08	
21–22 days old	2.65 ± 0.05	
31–42 days old	2.55 ± 0.05	

Several methods exist to assay total CSF protein. These include turbidometric, spectrophotometric, Lowry, biuret, dye binding, and immunologic methods.[18] Each of these methods has different characteristics of sensitivity and specificity and will generate slightly different assay results. Hence, it is important for the practitioner to utilize reference ranges reported by the particular laboratory that is performing the assay. The wide range of normal equine CSF total protein values that have been reported in the literature is largely a function of the various methods used, as well as interhorse variability. Values from 10 to 120 mg/dl in healthy horses have been reported[13,18] although the commonly reported reference range is 50–100 mg/dl.[18] The total protein concentration also differs depending upon the site of collection, with samples collected from the lumbosacral site having a slightly higher concentration than that from the AO site.[13,26] In one study, the CSF total protein from the LS space was reported as 63.9 mg/dl (95% CI 54.7;73.0 mg/dl), while the mean total protein from the same horses from the AO site was 53.2 mg/dl (95% CI 45.2;61.3 mg/dl).[26] In addition to the site of collection, it has been reported by one investigator that ponies have a higher CSF total protein than horse breeds (37.2 vs. 60.5 mg/dl).[13] Breed-related differences have not been further examined and substantiated, however. The CSF total protein concentration of foals is higher than that of normal adult horses.[19,27] Newborn foals (i.e., less than 2 days of age) had a mean CSF total protein of 109.0 mg/dl, with this value decreasing to adult values by the time the foals were 21 days of age.[19]

An increase in CSF total protein is the single most useful change in the chemical composition of the CSF.[17] Protein concentrations are increased in diseases of the nervous system and occur due to increased permeability of the blood–CSF or BBB, increased protein synthesis within the CNS, obstruction of CSF flow, or tissue degeneration/necrosis. Obstructive diseases result in high protein concentrations due to enhanced resorption of water, as well as protein leakage. Complete spinal fluid block is associated with very high CSF protein concentrations and is referred to as "Froins syndrome." Low CSF protein is rarely found but can occur due to CSF leakage, removal of excessive quantities of CSF, increased ICP, or in cases of water intoxication.

The nature of specific proteins in equine CSF has been investigated by means of protein electrophoresis.[26,28,29] These studies found that the electrophoretogram varied based on the supporting matrix used. When compared to protein electrophoresis of serum, CSF demonstrates a small pre-albumin peak, and the small α bands seen in serum are indistinct. The clinical significance of the pre-albumin peak is not known. In one study comparing the CSF electrophoresis of normal horses and horses with cervical compressive myelopathy, differences were detected in affected horses. Post-β peaks were observed in 10 of 14 horses with cervical compression, and in none of the normal horses.[26] In addition, the β-globulin fraction (composed of transferrin, plasminogen, complement, and hemopexin) was less in horses with cervical compression than normal horses. While these changes were suggested as a possible diagnostic method to screen for horses with cervical compressive disease, further work has not been pursued, and this technique is not used clinically at this time (Table 2.4).

Electrolyte composition of the CSF has been only sparsely reported, but in general, the CSF sodium and chloride concentrations are similar to or slightly higher than serum values, while the potassium concentration is similar to or slightly lower than serum concentrations.[13,19,27] Magnesium concentration is slightly higher in CSF when compared to blood concentrations.[19] There does not appear to be any age-related effect upon electrolyte composition of the CSF in foals.[19] Measurement of electrolyte concentration has not been reported to be of utility in the diagnosis of neurologic disease in horses.

CSF glucose concentration is closely correlated with blood glucose concentration and enters the CSF by both active transport and passive diffusion.[25] A maximum CSF glucose concentration of about 200 mg/dl is proposed,[25] but this has not been evaluated in the horse. Normal values for the horse are 35–75% of plasma glucose and are usually found to be 30–70 mg/dl for the AO site and 40–75 mg/dl for the LS site. It is best to evaluate CSF glucose concentrations in concert with plasma or serum glucose concentration; however, there is a temporal delay of 1 to 3 h in changes of CSF glucose concentration following changes in plasma concentration.[18]

Decreased concentration of CSF glucose (hypoglycorrhachia) is caused by hypoglycemia, decreased active transport, and/or increased utilization. Bacterial meningitis is the most commonly recognized condition leading to increased utilization. This

Table 2.4. Protein Fractions in Equine Cerebrospinal Fluid

Protein Fraction	AO[21]	LS[21]	AO[24]	AO[23]
Total protein (mg/dl) (95% CI)	53.2 ± 3.8 (45.2;61.3)	63.9 ± 0.1 (54.7;73.0)	9.2 ± 3.7	40.1 ± 0.1 (34.1;46.2)
Pre-albumin (mg/dl) (95% CI)	1.3 ± 0.2 (.94;1.6)	1.9 ± 0.2 (1.4;2.4)	0.19 ± 0.2	Not reported
Albumin (mg/dl) (95% CI)	20.3 ± 1.6 (17.0;23.5)	24.3 ± 0.5 (21.0;27.6)	3.99 ± 1.68	15.3 ± 1.2 (12.9;17.6)
α1 globulin (mg/dl) (95% CI)	1.8 ± 0.3 (1.2;2.4)	1.9 ± 0.4 (0.9;2.8)	0.48 ± 0.24	5.2 ± 0.9 (3.5;6.9)
α2a (mg/dl) (95% CI)	Not reported	Not reported	0.31 ± 0.15	6.7 ± 0.4 (6.0;7.4)
α2bc (mg/dl) (95% CI)	Not reported	Not reported	0.59 ± 0.31	Not reported
β1 globulin (mg/dl) (95% CI)	4.6 ± 0.5 (3.5;5.8)	6.0 ± 0.7 (4.6;7.5)	1.59 ± 0.75	5.8 ± 0.6 (4.7;7.4)[a]
β2 globulin (mg/dl) (95% CI)	10.9 ± 0 .9 (8.8;12.8)	14.5 ± 1.1 (12.0;16.9)	0.7 ± 0.32	Not reported
γ globulin (mg/dl) (95% CI)	14.2 ± 0.5 (11.1;17.3)	15.3 ± 1.5 (12.0;18.6)	1.35 ± 0.57	5.7 ± 0.8 (4.6;7.3)

[a] Values reported as β globulins only.

arises due to the combined effects of increased leukocyte metabolism, consumption of glucose by bacteria, and increased metabolic rate of CNS tissue. Erythrocytes also utilize glucose, and subarachnoid hemorrhage may be associated with decreased CSF glucose concentration.

Lactic acid is produced by the anaerobic metabolism of glucose, and increased CSF lactate concentrations have been found to be associated with bacterial meningitis, EEE, head trauma, and brain abscesses.[30] Lactic acid is ionized and does not cross the BBB, while the lactate salt does diffuse across the blood–CSF barrier into the CSF. Reference ranges for CSF lactate have been described as well as values in various equine neurologic illnesses.[18,30] A mild elevation (but not statistically significantly different from controls) in CSF lactate concentration was found in foals with bacterial meningitis.[30] The use of CSF lactate and glucose concentrations to diagnose foals with bacterial meningitis is complicated by the fact that most of such foals are hypoglycemic and in circulatory shock and may have an elevated blood lactate in the absence of CNS disease.

Homeostatic mechanisms are present which contribute to the maintenance of a constant pH in the CSF and extracellular fluid of the nervous system. CSF pH remains stable over a fairly wide range of blood pH and is influenced by the function of the BBB. In addition, hydrogen ion-sensitive chemoreceptors present in the brainstem regulate respiration with direct effect upon arterial, and subsequently CSF, pH. The carbon dioxide/bicarbonate system is the major buffer in the CSF, due to the very low total protein present.[17,31] In a group of healthy neonatal foals, the CSF was slightly more acidic (7.389) than corresponding arterial (7.452) or venous blood (7.422).[31] The CSF PCO_2 (37.8 mm Hg) was slightly greater than the corresponding arterial blood (36.6 mm Hg) and slightly less than the corresponding venous blood (39.9 mm Hg).[31] Acidity of CSF increased, associated with an increased CSF PCO_2 after 75 min of hypercapnia. The authors concluded that the buffering capacity of the CSF is poor, related to the low protein concentration and the relatively poor permeability of the blood–CSF barrier.[31]

The differing solubility of the BBB and blood–CSF barriers to CO_2 (high) and bicarbonate (low) can lead to unexpected changes in CSF pH in response to blood pH changes. Changes in the arterial CO_2 tension result in changes in CSF pH which parallel that of the blood.[17,31] An abrupt increase in blood bicarbonate concentration, such as that

associated with intravenous infusion of sodium bicarbonate to treat acidosis for example, can result in a paradoxical decrease in CSF pH due to the rapid movement of CO_2 into the CSF and the slower accumulation of bicarbonate. These paradoxical reactions are usually transient and last only a few minutes to hours.[17] Their significance in clinical practice is unknown, and they may be only laboratory curiosities.

A number of enzymes have been reported to be present in the CSF and to have diagnostic and clinical utility. The most commonly discussed in the equine literature include creatine kinase (CK), lactate dehydrogenase (LDH), alkaline phosphatase (AP), and aspartate transaminase (AST). As most enzymes are relatively large molecules, there is very little diffusion across an intact and normal blood–CSF barrier, and increased concentrations of enzymes in the CSF are assumed to have arisen from the CNS. Potential sources of the increased enzyme activity in the CSF include diffusion across a damaged BBB or blood–CSF barrier, release of enzymes from cells within the CNS such as inflammatory cells, microorganisms, and tumors, or directly from damaged nerve cells and myelin.

CK exists as three isoenzymes—CK-MM (CK1) for muscle, CK-MB (CK2) for cardiac muscle, and CK-BB (CK3) for nervous tissue. The CSF_{ck} has been reported to be a sensitive, but non-specific marker of nervous system disease.[32,33] In humans, many conditions including trauma, inflammatory disease, global ischemia, microemboli, and tumors have been associated with increased concentration of CSF_{ck}.[34–36] Reference ranges for equine CSF_{ck} concentrations have been described; however proper validation of the assay in CSF is lacking. CSF_{ck} activity is typically very low, and increased values have been associated with neurologic disease in horses.[37,38] In foals, increased CSF_{ck} was observed when compared to values in adults.[27] Increased CSF_{ck} activity was reported in horses with EPM, while CSF_{ck} activity in horses with cervical compressive myelopathy was within the reference range (i.e., below 6 IU/l).[37] The authors suggested that CSF_{ck} values may therefore have value in the evaluation of horses with neurologic disease. Others have questioned this assessment and have found increased CSF_{ck} concentrations in horses following traumatic taps and in CSF samples contaminated with epidural fat.[39] Thus, contaminated CSF samples or those arising from difficult taps clearly have limitations, and increased enzyme activity in these cases should be interpreted with caution. However, CSF_{ck} may be a valid marker of CNS disease in CSF samples that are not contaminated or result from a spinal tap that require multiple attempts.

Reference ranges for LDH and AP have been reported for the adult horse and are considered to be less than 8 IU, with a mean of 1.54 and 0.8 IU, respectively.[13] AST has also been reported in equine CSF, with a mean activity of 30.7 Sigma-Frankel (SF) units. In foals, the concentration of these enzymes was higher than in a group of adults.[27] These enzymes have been very poorly studied in the horse, and little information is available regarding their evaluation in horses with neurologic disease. One report suggests that increased LDH activity may occur in horses with spinal lymphosarcoma.[40]

The concentration of cholesterol and lipoproteins in equine CSF has been determined. Mean CSF cholesterol in mares was 13.56 mg/ml (9.8–17.5).[41] Two major lipoproteins were detected in the CSF of horses: apolipoprotein A-1 (ApoA-1) and apolipoprotein E (apoE).[41] The role of these compounds in the physiology of the nervous system is undetermined in the horse; however, these compounds are known to interact with a variety of receptors within the nervous system and presumably influence function and/or neuronal health. A number of fatty acids are also present in the CSF of normal horses. Isobutyric, isovaleric, phenylacetic, lauric, myristic, palmitic, oleic, and stearic acids were uniformly present in both normal horses and horses with neurologic disease.[42] Oleic, palmitic, and stearic acids predominated in equine CSF, and no changes in the fatty acid profile could be detected in neurologically abnormal horses.[42] Hence, evaluation of CSF fatty acid profile appears to have little clinical value in equine neurologic disease.

Not surprisingly, a number of neurotransmitter compounds can found be within the CSF of horses, the primary compounds being homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA).[43] Younger animals had greater CSF concentration of HVVA than 5-HIAA, and mature horses had lower concentrations of CSF HVA than juvenile horses.[44] These compounds have not been investigated in horses with clinical disease at this time, and their utility in clinical medicine is undetermined.

REFERENCES

1. Banks WJ. 1981. Nervous System. In *Applied Veterinary Histology*, edited by Banks WJ, 277–303. Baltimore: Williams and Wilkins.
2. Masserman JH. 1934. Cerebrospinal fluid hemodynamics. IV. Clinical experimental studies. *Arch Neurol Psychiatr* 32:523–53.
3. Rubin RC. 1966. The production of cerebrospinal fluid in man and its modification by acetezolamide. *J Neurosurg* 25:430–6.
4. Fishman RA. 1992. Physiology of the cerebrospinal fluid. In *Cerebrospinal Fluid in Diseases of the Nervous System*, edited by Fishman RA, 23–42. Philadelphia: W.B. Saunders Co.
5. Brigham MW. 1977. Morphology of the blood–brain interfaces. *Exp Eye Res* 25:1–25.
6. Pardridge WM, Oldendorg WH, Cancilla P, *et al*. 1986. Blood–brain barrier: Interface between internal medicine and the brain. *Ann Int Med* 105:82–95.
7. Gross PM, Weindl S. 1987. Peering through the windows of the brain. *J Cereb Blood Flow Metab* 7:663–72.
8. Andrews F, Maddux J, Faulk B. 1990. Total protein, albumin quotient, IgG and IgG index determinations for horse cerebrospinal fluid. *Prog Vet Neurol* 1:197–204.
9. Gollob E, Edinger H, Stanek C, *et al*. 2002. Ultrasonographic investigation of the atlanto-occipital articulation in the horse. *Equine Vet J* 34:44–50.
10. Audigie F, Tapprest J, Didierlaurent D, *et al*. 2004. Ultrasound-guided atlanto-occipital puncture for myelography in the horse. *Vet Radiol Ultrasound* 45:340–4.
11. Aleman M, Borchers A, Kass PH, *et al*. 2007. Ultrasound-assisted collection of cerebrospinal fluid from the lumbosacral space in equids. *J Am Vet Med Assoc* 230:378–84.
12. Regodon S, Franco A, Lignereux Y, *et al*. 1993. A new technique for accessing the cerebral ventricles of the horse. *Res Vet Sci* 55:389–91.
13. Mayhew IG, Whitlock RH, Tasker JB. 1977. Equine cerebrospinal fluid: reference values of normal horses. *Am J Vet Res* 38:1271–4.
14. Moore RM, Trim CM. 1993. Effect of hypercapnia or xylazine on lateral ventricle and lumbosacral cerebrospinal fluid pressures in pentobarbitol-anesthetized horses. *Vet Surg* 22:151–8.
15. Brosnan RJ, LeCouteur RA, Steffey EU, *et al*. 2002. Direct measurement of intracranial pressure in adult horses. *Am J Vet Res* 63:1252–6.
16. Kortz GD, Madigan JE, Goetzman BW, *et al*. 1995. Intracranial pressure and cerebral perfusion pressure in clinically normal equine neonates. *Am J Vet Res* 56:1351–5.
17. Fishman RA. 1992. Composition of the cerebrospinal fluid. In *Cerebrospinal Fluid in Diseases of the Nervous System*, edited by Fishman RA, 183–252. Philadelphia: W.B. Saunders.
18. Green E, Constantinescu G, Kroll R. 1993. Equine cerebrospinal fluid: Analysis. *Compend Contin Educ Pract Vet* 15:288–301.
19. Furr M, Bender H. 1994. Cerebrospinal fluid variables in clinically normal foals from birth to 42 days of age. *Am J Vet Res* 55:781–4.
20. Beech J. 1983. Cytology of equine cerebrospinal fluid. *Vet Pathol* 20:553–62.
21. Darian BJ, Belknap J, Nietfeld J. 1988. Cerebrospinal fluid changes in two horses with central nervous system nematodiasis (*Micronema deletrix*). *J Vet Intern Med* 2:201–5.
22. Furr M, MacKay R, Granstrom D, *et al*. 2002. Clinical diagnosis of equine protozoal myeloencephalitis (EPM). *J Vet Intern Med* 16:618–21.
23. Wilson JW, Stevens JB. 1977. Effects of blood contamination on cerebrospinal fluid analysis. *J Am Vet Med Assoc* 171:256–60.
24. Sweeney CR, Russell GE. 2000. Differences in total protein concentration, nucleated cell count, and red blood cell count among sequential samples of cerebrospinal fluid from horses. *J Am Vet Med Assoc* 217:54–7.
25. Kjeldsberg CR, Krieg AF. 1984. Cerebrospinal fluid and other body fluids. In *Clinical Diagnosis and Management by Laboratory Methods*, edited by Henry JB, 459–90. Philadelphia: W.B. Saunders Co.
26. Furr M, Chickering WR, Robertson J. 1997. High resolution protein electrophoresis of equine cerebrospinal fluid. *Am J Vet Res* 58:939–41.
27. Rossdale PD, Cash RSG, Leadon DP. 1982. Biochemical constituents of cerebrospinal fluid in premature and full term foals. *Equine Vet J* 14:134–8.
28. Kirk GR, Neate S, McClure RC, *et al*. 1974. Electrophoretic pattern of equine cerebrospinal fluid. *Am J Vet Res* 35:1263–4.
29. Kristensen F, Firth EC. 1977. Analysis of serum proteins and cerebrospinal fluid in clinically normal horses, using agarose electrophoresis. *Am J Vet Res* 38:1089–92.
30. Green EM, Green SL. 1990. Cerebrospinal fluid lactic acid concentrations: Reference values and diagnostic implications of abnormal concentrations in adult horses. *Proc 18th Annual Meeting ACVIM* 495–9.
31. Geiser DR, Andrews F, Rohrbach BW, *et al*. 1996. Cerebrospinal fluid acid–base status during normocapnia and acute hypercapnia in equine neonates. *Am J Vet Res* 57:1483–7.

32. Wilson JW. 1977. Clinical application of cerebrospinal fluid creatine phosphokinase determination. *J Am Vet Med Assoc* 171:200–2.
33. Mass AI. 1977. Cerebrospinal fluid enzymes in acute brain injury. *J Neurol Neurosurg Psychiatry* 40:655–65.
34. Nathan MJ. 1967. Creatine phosphokinase in the cerebrospinal fluid. *J Neurol Neurosurg Psychiatry* 30:52–4.
35. Vaagenes P, Kjekshus J, Siversten E, *et al*. 1987. Temporal patterns of enzyme changes in cerebrospinal fluid in patients with neurologic complications after open heart surgery. *Crit Care Med* 15:726–31.
36. Rabow L, DeSalles AF, Becker DP, *et al*. 1986. CSF brain creatine kinase levels and lactic acidosis in severe head injury. *J Neurosurg* 65:625–9.
37. Furr MO, Tyler RD. 1990. Cerebrospinal fluid creatine kinase activity in horses with central nervous system disease: 69 cases (1984–1989). *J Am Vet Med Assoc* 197:245–8.
38. Furr MO, Anver M, Wise M. 1991. Intervertebral disk prolapse and diskospondylitis in a horse. *J Am Vet Med Assoc* 198:2095–6.
39. Jackson C, DeLahunta A, Divers TJ, *et al*. 1996. The diagnostic utility of cerebrospinal fluid creatine kinase activity in the horse. *J Vet Intern Med* 10:246–51.
40. Andrews FM, Reed SM. 1990. The ancillary techniques and tests for diagnosing equine neurologic disease. *Vet Med* December:1325–30.
41. Puppione DL, MacDonald MH. 2002. Characterization of lipoproteins in cerebrospinal fluid of mares during pregnancy and lactation. *Am J Vet Res* 63:886–9.
42. Sweeney RW, Beech J, Whitlock RH, *et al*. 1989. Analysis of fatty acids in equine cerebrospinal fluid using gas chromatography with electron capture detection. *J Chromatogr* 494:278–82.
43. Vaughn DM, Smyth GB. 1989. Different gradients for neurotransmitter metabolites and protein in horse cerebrospinal fluid. *Vet Res Commun* 13:413–9.
44. Vaughn DM, Smyth GB, Whitmer WL, *et al*. 1989. Analysis of equine cisterna magna cerebrospinal fluid for the presence of some monamine neurotransmitters and transmitter metabolites. *Vet Res Commun* 13:237–49.

3
Immunology of the Central Nervous System

Martin Furr

It has been known for many years that the immune response of the central nervous system (CNS) differs from that in peripheral tissues. Foreign tissue transplanted into the brain survives for much longer than when the same tissue is transplanted into a peripheral tissue.[1] This led to the designation of the brain and CNS as an "immune privileged site," that is, a tissue in which the immune response to foreign antigen is inhibited.[2] Other immune privileged sites include the feto-placental unit, the anterior chamber of the eye, and the testis. It is presumed that this mechanism of active immunosuppression has a survival role. Functional immunosuppression within the CNS is a means to limit the extent of inflammation and increase the likelihood of return to normal function of neurons and the CNS. As Leslie Brent states "… It may be supposed that it is beneficial to the organism not to turn the anterior chamber of the eye, or the brain, into an inflammatory battlefield, for the immunological response is sometimes more damaging than the antigen insult that provoked it…."[3] This observation concisely and elegantly summarizes the importance of immunosuppression and control of inflammation in patients with inflammatory disease of the CNS.

The CNS is not, however, immunologically inept. This tissue can and does mount an effective immune response. This is supported by the observation that while tissue grafted into the CNS survives for prolonged periods, the tissue will be promptly rejected if the subject is immunized by prior exposure.[1] The specific characteristics of the immune response of immune privileged sites differ from those of other tissues. Specifically, antigen-specific inhibition of delayed-type hypersensitivity is induced, as well as an increased production of antigen-specific antibody.[4,5]

Initial interpretation of the diminished CNS immunoreactivity was attributed to the lack of conventional lymphatic vessels within the CNS. This was believed to isolate any antigen within the CNS from the peripheral immune system. Recent findings, however, indicate that there is significant contact of CNS antigen with the peripheral immune system. Up to 47% of antigen injected into the CNS appears in cervical lymph and deep cervical lymph nodes.[6] Also, when antigen is directly placed within the CNS, antigen-specific antibodies appear in the serum, and antigen can be recovered in the deep cervical lymph nodes following injection.[7,8]

Another functional explanation for immune privilege within the CNS is the low concentration of major histocompatibility complex (MHC) class II molecules expressed on cells of the CNS. As antigen presentation is required to initiate an adaptive immune response, the lack of antigen-presenting cells within the CNS has been considered to be a key factor in the dampened immune response observed following CNS infection. Although there is little constitutive secretion of MHC class II molecules, many cells of the CNS have been found to express MHC class II molecules when appropriately stimulated. In addition to escape from the CNS, soluble antigen can be presented to lymphocytes in the bloodstream by brain endothelial and choroid plexus cells,[9] brain microvessel smooth muscle cells,[10] as well as astrocytes and microglia.[11,12] In addition, B cells are potent antigen-presenting cells.[13]

Another feature of the CNS and cerebrospinal fluid (CSF) that contributes to a diminished immune response is the observation that concentrations of complement are almost undetectable in normal healthy human subjects.[14] This has not been determined in the horse but is likely to be similar to other species.

The nervous system parenchyma consists largely of two fixed cell populations—neurons and glial cells. Neuron function is restricted to conduction of electrical information, while glial cells have a supportive function. Glial cells differ from neurons in their lack of synaptic contacts, and they maintain the property of mitosis throughout life, and in particular as a response to injury.[15] Glial cells are subdivided into macroglia and microglia (Table 3.1).

Microglia are of mesodermal origin and invest the CNS at the time of embryonic vascularization of the CNS. Microglia maintain mobility, which is essential in responding to inflammation. They migrate to areas of inflammation and are involved in phagocytosis, antigen presentation, and the production and release of inflammatory mediators. The mediators have an auto, para, and possibly endocrine function, which signal to other cell populations (lymphocytes, polymorphonuclear cells, and astrocytes). Microglia are part of the reticuloendothelial system (RES) and are related in origin, function, and morphology to monocytes.[12] It is thought that they form a resident population of cells of the RES within the CNS. Whether there is a truly sequestered population of RES cells in the CNS or whether they are continuously replaced by blood-derived progenitors is not clearly understood.

Table 3.1. Functional Classification of Cells of the Central Nervous System (CNS)

Cell Type	Function
Macroglia	
Oligodendrocyte	Produces myelin in CNS
Schwann cell	Produces myelin in peripheral nervous system
Astrocyte	Antigen-presentation Neurotransmitter recycling
Microglia	Antigen-presentation Phagocytosis
Neuron	Conduction of electrical impulses

Macroglia consists of astrocytes and oligodendrocytes which are of ectodermal origin. Oligodendrocytes are responsible for the production of myelin within the CNS. The immunologic role of oligodendrocytes is less well defined. Oligodendrocytes appear to have limited ability to express MHC class II receptors, but they can produce interleukin-1 (IL-1).[16] The immunologic function of astrocytes is also incompletely understood. The perivascular end plates, or "foot processes" of astrocytes ensheath the cerebral vasculature, restricting the passage of macrophages and other immune responsive cells, yet allowing the passage of activated T cells. As astrocytes are positioned at the interface between blood and the CNS, they can also influence the activity of invading cells.[17] Astrocytic responses can be detected within 24 h after a CNS infection or inflammatory event.[18] Astrocytes respond to the presence of IL-1 with the production of interferon-γ (IFN-γ) and expression of MHC II molecules.[19] Tumor necrosis factor alpha induces astrocytes to express intracellular adhesion molecule-1 (ICAM-1), which is necessary for cellular migration through the blood–brain barrier (BBB).[20] Hence, the astrocyte has a significant role in responding to and regulating immune responses within the CNS.

In healthy mammals, the CNS contains T lymphocytes in such low concentrations that they are almost undetectable by immunohistochemical methods, yet are readily found in various inflammatory diseases.[21] B and T lymphocytes were noted in very low numbers in the spinal cord of normal horses (1 and 2% of nucleated cells, respectively).[22] Lymphocyte numbers in CSF have also been examined, yet are present in very low numbers. In human CSF, T cells predominate and are present in slightly higher proportions than in peripheral blood (72.9 vs. 63.8%, respectively).[23] The proportion of B cells in human CSF varies among authors from <1 to 16%.[23–25]

In the CSF of normal adult horses, T cells also predominate and are found in a higher proportion than in blood. The $CD4^+$ lymphocyte phenotype predominates and is present in slightly lower numbers than in peripheral blood, while the $CD8^+$ subset proportion is greater than in blood (13.6 vs. 23.4%).[26]

The mechanisms by which lymphocytes are normally excluded from the CNS, yet are permitted to

enter during disease, are poorly understood. The BBB is a functional and anatomical barrier between the CNS and the blood and acts as a significant barrier for cellular entry. Access to the CNS is strictly regulated, and the barrier guarantees a microenvironment that maintains CNS function. Increased permeability of the BBB is a pathologic event, which allows access of plasma proteins, complement factors, and inflammatory cells into the CNS. This is reflected as an increase in the albumin quotient (AQ), total protein, and cellularity of the CSF.

Even in the presence of a healthy BBB, there is a normal surveillance of the CNS by circulating lymphocytes, with fluorescein-labeled cells being found in CSF within 3 h of injection and peaking at 9–12 h after injection.[21] The time course for lymphocyte entry was similar for "activated" or unstimulated cells. In another study, it was found that lymphocytes enter the CSF in approximately the same time course as cells appear in the subcutaneous lymphatic fluid. Hence, it appears that cells do not need to be activated to allow entry into the CNS, and CNS lymphocytes appear to be a part of the normal recirculating pool.[27] In support of this concept, work in humans has found that CSF lymphocytes are primarily of memory phenotype ($CD45RO^+$) but show no evidence of recent activation.[25] Once primed cells recognize their cognate antigen within the CNS, however, they are retained and do not emigrate from the tissue, leading to a cellular pleocytosis within the CNS/CSF.

Of great clinical interest is the production of immunoglobulins (Igs) in the CNS/CSF (intrathecal Ig synthesis), as this body fluid is often used in immunodiagnostic assays for conditions such as equine protozoal myeloencephalitis (EPM). In the stereotypical humoral immune response, B lymphocytes require physical contact with a helper T cell to initiate their response to an antigen. This occurs via the interaction of MHC class II molecules and antigen. Additional costimulation is required and is provided via the interaction of CD19/CD21 receptors and the CD40/CD40L receptors.[28] In peripheral tissues, this physical contact is accomplished by the interaction of B and T cells in lymph nodes. In neuroinflammatory disease or neuroinfections, the mechanism of antigen-specific activation of lymphocytes requires that processed antigen leaves the CNS and consequently activates its antigen-specific lymphocytes outside the CNS, in lymph nodes draining the CNS intracellular fluid, and CSF. Cells then traffic back into the CNS, under the influence of local adhesion factors, for local (intrathecal) Ig production. Once exposed to an antigen, memory B cells remain within the CNS and direct intrathecal activation of plasma cell with antibody production (Figure 3.1).[13]

Ig concentrations in the CSF of normal horses was reported to be 10.2 ± 5.5 mg/dl (mean ± SD) from the atlanto-occipital (AO) space and 9.9 ± 5.7 mg/dl from the lumbosacral (LS) space in foals less than 10 days of age.[29] In normal adult horses, CSF IgG concentration was 18.5 ± 1.4 mg/dl (mean ± SD) in fluid collected from the AO space.[8] In another study, CSF IgG concentrations in normal adult horses was reported to be 0.056 ± 0.014 g/l (i.e., 5.6 ± 1.4 mg/dl) (mean ± SD).[30] The concentration of other Ig subtypes has not been reported. Given that the normal serum concentration of IgG was 2740 ± 286 mg/dl (mean ± SEM) in one study, it is clear that there is a relative paucity of Ig in the CNS and CSF in health.[8] Following neuroinfection, the concentration of Ig increases, with most Ig subtypes represented.[31–33] It has been suggested that isotype switching does not occur in the CNS,[34] yet clear evidence of isotype switching of B cells within the CNS has been documented in a model of viral encephalitis in mice.[35] Presumably, this also occurs in horses but has not been specifically investigated.

A number of methods have been proposed for the quantitative discrimination between a pathological CNS-derived (i.e., intrathecal) Ig production and that which arises within the CSF from blood and protein leakage across a damaged BBB.[36] This distinction is of particular importance in the interpretation of diagnostic tests for neuroinfections, such as EPM.

In equine medicine, the IgG_{index} is the most commonly discussed method for estimating the excess amount of IgG within the CSF in disease of the nervous system.[29,30] The IgG_{index} is a unitless number and is based on the concept that the amount of IgG in the CSF is proportional to the amount of IgG in the serum and is hence dependent upon the barrier function of the BBB, as reflected by the AQ. This proportionality can be determined mathematically and related by the equation:

$$IgG_{index} = \frac{IgG_{csf}}{IgG_{serum}} \times \frac{Albumin_{serum}}{Albumin_{csf}}$$

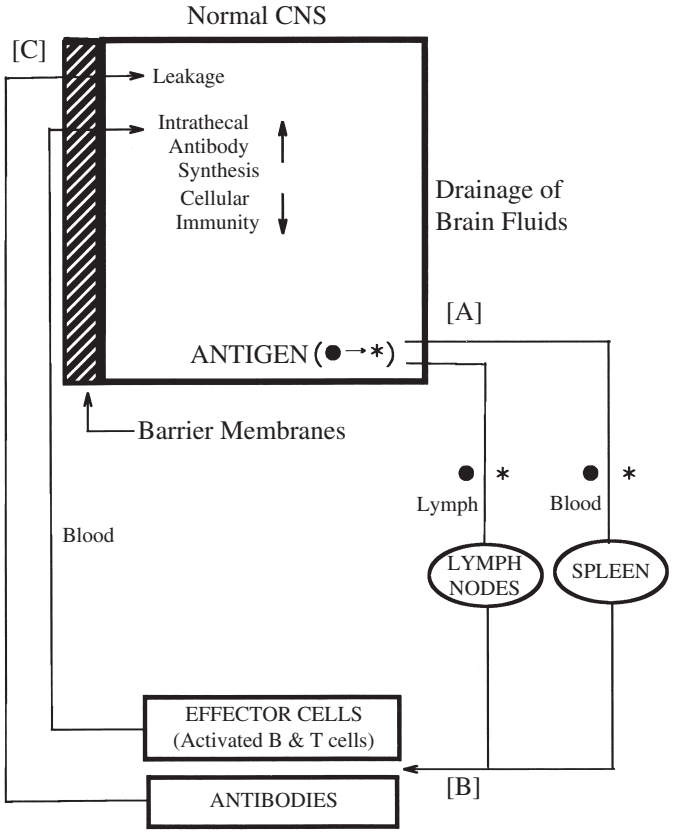


Figure 3.1. Schematic diagram illustrating pathways leading to interaction between antigens (*) from the normal central nervous system (CNS) and extracerbreal lymphoid organs (afferent arm) (designated [A]). This interaction generates antigen-specific, activated effector cells and antibodies (designated [B]). The immune response loop is completed by the transbarrier movement of activated immune cells across intact brain–barrier membranes and antibody leakage across nonbarrier sites (efferent arm, designate [C]). Brain-barrier membranes consist of the cerebral endothelium, choroidal epithelium, and arachnoid. The scheme recognizes the possibility that antigens in the brain are processed in some way yet to be established. Reprinted with permission from Cserr HF, Knopf PM. 1997. Cervical lymphatics, the blood–brain barrier, and the immunoreactivity of the brain. In *Immunology of the Central Nervous System*, edited by Keane RW, Hickey WF, 134–152. New York: Oxford University Press.

From a study of normal adult horses, a value of 0.194 ± 0.046 (mean ± SD) was determined for CSF from the AO space and 0.194 ± 0.05 (mean ± SD) for the LS space.[30] From this study, an IgG_{index} value of greater than 0.27 was proposed to reflect intrathecal Ig synthesis.[30] For neonatal foals, an IgG_{index} of 0.519 ± 0.284 (mean ± SD) (AO site) and 0.482 ± 0.270 (mean ± SD) (LS site) was reported.[29] In another study, the IgG_{index} in normal adult horses was 0.45 ± 0.01 (mean ± SEM).[8] The application of the IgG_{index} has not been rigorously applied to the evaluation of horses with CNS disease. In a model of neuroinflammation of the horse, the IgG_{index} did increase dramatically after antigen challenge of the CNS (Furr, unpublished data). The IgG_{index} has been examined in horses with EPM, and

conflicting results have been reported. In one large study of EPM (101 horses), it was found that the IgG_{index} was greater in horses with EPM than reported normal values, and the magnitude of the IgG_{index} decreased during treatment and recovery.[37] Owing to its non-specific nature, the IgG_{index} is currently considered to have little value in the diagnosis of EPM however.[38]

Other techniques that have been proposed to evaluate intrathecal antibody synthesis in the horse include the Goldman–Witmer coefficient (*C* value) and the antibody index (AI). These methods have been proposed to be more sensitive and specific for diagnostic purposes than the IgG_{index} because they are calculated using antigen-specific Ig titers.[38] These are similar techniques which are based on the premise that in the presence of a normal BBB and no intrathecal antibody production, the ratio of antigen-specific CSF IgG to total IgG (or albumin concentration) in CSF will remain similar to the corollary ratio in serum. Hence, any passive movement of Ig across the BBB would result in a ratio of less than or equal to 1. Intrathecal Ig production results in a disproportionately greater production of Ig in the CSF than serum, resulting in a calculated value greater than 1. The two methods differ only in the reference protein used; the AI uses albumin while the *C* value uses total IgG. Empiric evaluation of these indices in the horse is limited; however actual values in normal horses extend up to 1.7 in some animals.[8] This probably reflects assay error, as determination of some values is difficult. The formulas for calculation of the AI and *C* value are:

$$\text{AI} = \frac{\text{QAb}}{\text{QAlb}}$$

where QAb (antibody quotient) is reciprocal CSF $\text{titer}_x \times 1000$/reciprocal serum titer_x and QAlb (albumin quotient) is (CSF albumin concentration/serum albumin concentration) × 1000 (Figure 3.2).

$$C \text{ value} = \frac{\text{Reciprocal CSF titer}_x \times \text{total serum IgG}}{\text{Total CSF IgG} \times \text{reciprocal serum titer}_x}$$

It is obvious that the CNS has the functional capacity to respond to antigen, yet the response is altered, suggesting an active regulatory mechanism for immune privilege. The recognition that there were numerous immunoregulatory compounds (cytokines) responsible for the elegant coordination of the immune response has led to a search for such compounds within immune privileged tissues which might explain the observed phenomenon.

Within the CNS, and with an intact BBB, upregulation of the effector arm of the immune system differs from other sites of the body. One strategy employed in immune privileged sites is to create a local immunosuppressive microenvironment. This inhibitory milieu appears to be contributed to in part by immunosuppressive cytokines and substances

Patient Values:

	Normal	Neuroinflammation
Serum IgG	2420	3565
Serum Albumin	2350	3206
Serum Titer X	1:256	1:512
CSF IgG	17.3	288.6
CSF Albumin	28.6	128.6
CSF Titer X	1:2	1:128

Normal Horse:

$$\text{AI} = \frac{2 \times 1000/2.56}{(28.6/2350) \times 1000} = \frac{7.8}{12.1} = 0.64$$

$$C \text{ value} = \frac{2 \times 2420}{17.3 \times 256} = \frac{4840}{4428} = 1.1\text{n}$$

Horse with Neuroinflammation:

$$\text{AI} = \frac{128 \times 1000/512}{(128.6/3206) \times 1000} = \frac{250}{40} = 6.25$$

$$C \text{ value} = \frac{128 \times 3565}{288.6 \times 512} = \frac{456320}{147763} = 3.1$$

Values substantially greater than 1 in the horse with neuroinflammation confirms intrathecal production of antigen specific antibody for antigen X. *C* value and A1 often differ, and are rarely exactly the same.

Figure 3.2. Example calculations for determining the antibody index and *C* value for equine cerebrospinal fluid.

present in biological fluids that bathe these sites. There are multiple mechanisms by which T-cell-mediated processes can be suppressed. Responding lymphocytes can become functionally inactivated, or inactivated by initiating apoptotic cell death. A range of soluble substances have been identified, which have an *in vivo* and/or *in vitro* effect on the cells involved in defense mechanisms. Several substances with immunosuppressive properties were identified in brain tissue or CSF: alpha-melanocyte-stimulating hormone (α-MSH), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGrP), somatostatin, and the cytokine transforming growth factor-β (TGF-β), IL-4, and IL-10.[39,40] Of these potential factors, only TGF-β has been investigated in the horse.

A pleiotropic hormone, TGF-β, has the ability to influence many aspects of the immune response, including growth and differentiation of many hematopoetic lineages, proliferation and migration of mature immune cells, and regulation of immune responses.[41] For example, TGF-β inhibits IL-2-dependent proliferation, as well as secretion of IFN-γ, TNF-α, and -β, and IL-1, -2, and -3.[41,42] TGF-β suppresses MHC class II expression on cells induced by IFN-γ, thereby blocking one of the most important functions of IFN-γ.[42] While the predominant effect of TGF-β is immunosuppressive, it can lead to T-cell proliferation, block Fas-induced apoptosis, and expand the T_h2 $CD4^+$ T-cell subset via inhibition of T_h1 products.[42]

While not routinely found in the normal human adult brain tissue, TGF-β is found in the CNS in a variety of disease states, including multiple sclerosis, Alzheimer's disease, and stroke. In the diseased brain, the source of TGF-β has been considered to arise from infiltrating T cells and macrophages, although it is now evident that microglia, astroglia, and neurons can all produce at least some of the isoforms of TGF-β.[43]

It has been demonstrated that CSF will lead to suppressed lymphocyte blastogenesis and decreased IFN-γ production, and this effect was reversed by the application of anti-TGF antibodies.[39,40] In horses, TGF-β2 has been documented to be present in the CSF and will stimulate IFN-γ production, rather than suppress it as was found in other species.[44]

These findings confirm the immunomodulatory effects of CSF and suggest that immune privilege is maintained by the production of an immunosuppressive microenvironment. This environment is the product of the presence of immunosuppressive compounds within the CSF, combined with the presence of a BBB which mediates cellular infiltration into the CNS.[45] In general, the immune response within the CNS appears to be regulated in a manner that allows for control of infection, with a minimum of inflammation.

REFERENCES

1. Medewar P. 1948. Immunity to homologous grafted skin III. The fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. *Br J Exp Pathol* 29:58–69.
2. Barker C, Billingham R. 1977. Immunologically privileged sites. *Adv Immunol* 25:1–54.
3. Cserr HF, Knopf PM. 1992. Cervical lymphatics, the blood–brain barrier and the immunoreactivity of the brain: a new view. *Immunol Today* 13:507–12.
4. Kaplan HJ, Streilein JW. 1977. Immune response to immunization via the anterior chamber of the eye. *J Immunol* 118:809–14.
5. Panda J. 1965. Immunologic response to subarachnoid and intracerebral injections of antigens. *J Immunol* 94:760–4.
6. Cserr HF, Harling-Berg CJ, Knopf PM. 1992. Drainage of brain extracellular fluid into blood and deep cervical lymph and its immunological significance. *Brain Pathol* 2:269–76.
7. Harling-Berg C, Knopf PM, Merriam J, *et al.* 1989. Role of cervical lymph nodes in the systemic humoral immune response to human serum albumin microinfused into rat cerebrospinal fluid. *J Neuroimmunol* 25:185–93.
8. Furr M. 2002. Antigen-specific antibodies in cerebrospinal fluid after intramuscular injection of ovalbumin in horses. *J Vet Intern Med* 16:588–92.
9. Nathanson JA, Chun LL. 1989. Immunological function of the blood–cerebrospinal fluid barrier. *Proc Natl Acad Sci USA* 86:1684–8.
10. Fabry Z, Waldschmidt MM, Moore SA, *et al.* 1990. Antigen presentation by brain microvessel smooth muscle and endothelium. *J Neuroimmunol* 28:63–71.
11. Vidovic M, Sparacio SM, Elovitz M, *et al.* 1990. Induction and regulation of class II major histocompatibility complex mRNA expression in astrocytes by interferon-γ and tumor necrosis factor-α. *J Neuroimmunol* 30:189–200.
12. Hickey WF, Kimura H. 1988. Perivascular microglia are bone marrow derived and present antigen *in vivo*. *Science* 239:290–2.
13. Meinl E, Krumbholz M, Hohlfeld R. 2006. B Lineage cells in the inflammatory central nervous

system environment: migration, maintenance, local antibody production, and therapeutic modulation. *Ann Neurol* 59:880–92.
14. Cserr HF, DePasquale M, Harling-Berg CJ, *et al*. 1992. Afferent and efferent arms of the humoral immune response to CSF-administered albumins in a rat model with normal blood-brain barrier permeability. *J Neuroimmunol* 41:195–202.
15. Raine CS. 1994. Multiple sclerosis: immune system molecule expression in the central nervous system. *J Neuropathol Exp Neurol* 53:328–37.
16. Benveniste EN. 1998. Cytokine actions in the central nervous system. *Cytokine Growth Factor Rev* 9:259–75.
17. Aschner M. 1998. Immune and inflammatory responses in the CNS: modulation by astrocytes. *Toxicol Lett* 102:283–7.
18. Norenberg MD. 1996. Reactive astrocytosis. In *The Role of Glia in Neurotoxicity,* edited by Aschner M and Kimelberg HK, 93–107. Boca Raton: CRC Press.
19. Hellendall RP, Ting JP. 1997. Differential regulation of cytokine-induced major histocompatibility complex class II expression and nitric oxide release in rat microglia and astrocytes by effectors of tyrosine kinase, protein kinase C, and cAMP. *J Neuroimmunol* 74:19–29.
20. Frohman EM, Frohman TC, Dustin ML. 1989. The induction of intracellular adhesion molecule 1 (ICAM-1) expression on human fetal astrocytes by interferon-γ, tumor necrosis factor-α, lymphotoxin, and interleukin-1: relevance to intracerebral antigen presentation. *J Neuroimmunol* 23:117–24.
21. Hickey WF, Hsu B, Kimura H. 1991. T-lymphocyte entry into the central nervous system. *J Neuroscience Res* 28:254–60.
22. Scott PR, Witonsky S, Robertson J, *et al*. 2005. Increased presence of T lymphocytes in central nervous system of EPM affected horses. *J Parasitol* 91:1499–502.
23. Moser R, Robinson J, Prostko E. 1976. Lymphocyte subpopulations in human cerebrospinal fluid. *Neurology* 26:726–8.
24. Svenningsson A. 1993. Adhesion molecule expression on cerebrospinal fluid T lymphocytes: evidence for common recruitment mechanisms in multiple sclerosis, aseptic meningitis, and normal controls. *Ann Neurol* 34:155–61.
25. Svenningsson A. 1995. Lymphocyte phenotype subset distribution in normal cerebrospinal fluid. *J Neuroimmunol* 63:39–46.
26. Furr M, Pontzer C, Gasper P. 2001. Lymphocyte phenotype subsets in the cerebrospinal fluid of normal horses and horses with equine protozoal myeloencephalitis. *Vet Ther* 2:317–24.
27. Seabrook T, Johnston M, Hay J. 1998. Cerebral spinal fluid lymphocytes are part of the normal recirculating pool. *J Neuroimmunol* 91:100–7.
28. Tizard I. 1996. B cells and their response to antigen. In *Veterinary Immunology*, edited by Tizard I, 121–40. Philadelphia: W.B. Saunders, Co.
29. Andrews FM, Geiser DR, Sommardahl CS, *et al*. 1994. Albumin quotient, IgG concentration, and IgG index determinations in cerebrospinal fluid of neonatal foals. *Am J Vet Res* 55:741–5.
30. Andrews F, Maddux J, Faulk B. 1990. Total protein, albumin quotient, IgG and IgG index determinations for horse cerebrospinal fluid. *Prog Vet Neurol* 1:197–204.
31. Potasman I, Resnick L, Luft BJ, *et al.* 1988. Intrathecal production of antibodies against *Toxoplasma gondii* in patients with toxoplasmic encephalitis and the acquired immunodeficiency syndrome. *Ann Int Med* 108:49–51.
32. Knopf PM, Harling-Berg CJ, Cserr HF, *et al*. 1998. Antigen-dependent intrathecal antibody synthesis in the normal rat brain: tissue entry and local retention of antigen-specific B cells. *J Immunol* 161:692–701.
33. Tyor WR, Griffin DE. 1993. Virus specificity and isotype expression of intraparenchymal antibody-secreting cells during Sindbis virus encephalitis in mice. *J Neuroimmunol* 48:37–44.
34. Tipold A, Pfister H, Zurbriggen A, *et al.* 1994. Intrathecal synthesis of major immunoglobulin classes in inflammatory diseases of the canine CNS. *Vet Immunol Immunopathol* 42:149–59.
35. Tyor WR, Moench TR, Griffin DE. 1989. Characterization of the local and systemic B cell response of normal and athymic nude mice with Sindbis virus encephalitis. *J Neuroimmunol* 24: 207–15.
36. Lefvert AK, Link H. 1985. IgG production within the central nervous system: a critical review of proposed formulae. *Ann Neurol* 17:13–20.
37. Furr M, Kennedy T, MacKay R, *et al.* 2001. Efficacy of ponazuril 15% oral paste as a treatment for equine protozoal myeloencephalitis. *Vet Ther* 2:215–22.
38. Furr M, MacKay R, Granstrom D, *et al.* 2002. Clinical diagnosis of equine protozoal myeloencephalitis (EPM). *J Vet Intern Med* 16:618–21.
39. Wilbanks G, Streilein J. 1992. Fluids from immune privileged sites endow macrophages with the capacity to induce antigen-specific immune deviation via a mechanism involving transforming growth factor-β. *Eur J Immunol* 22:1031–6.
40. Taylor A, Streilein J. 1996. Inhibition of antigen stimulated effector T cells by human cerebrospinal fluid. *Neuroimmunomodulation* 3:112–8.

41. Letterio J, Roberts A. 1997. TGF-β; a critical modulator of immune cell function. *Clin Immunol Immunopathol* 84:244–50.
42. Derynck R, Choy L. 1998. Transforming growth factor-β and its receptors. In *The Cytokine Handbook*, edited by Thomson A, 593–636. New York: Academic Press.
43. Constam DB, Phillips J, Malipiero UV, *et al.* 1992. Differential expression of transforming growth factor-β1, -β2 and -β3 by glioblastoma cells, astrocytes, and microglia. *J Immunol* 148: 1404–10.
44. Furr M, Pontzer C. 2001. Transforming growth factor beta concentrations and interferon gamma responses in cerebrospinal fluid of horses with equine protozoal myeloencephalitis. *Equine Vet J* 33:721–5.
45. Streilein JW. 1993. Immune privilege as the result of local tissue barriers and immunosuppressive microenvironments. *Curr Opin Immunol* 5: 428–32.

4
Pharmaceutical Considerations for Treatment of Central Nervous System Disease

Martin Furr

Pharmaceutical treatment of diseases of the central nervous system (CNS) is occasionally necessary in equine practice. This includes treatment of bacterial, viral, fungal, or parasitic infections, the use of agents to minimize edema, and drugs to control or limit inflammation. The presence of the blood–brain barrier (BBB) (Section 1, Chapter 2) is of particular importance to CNS pharmacology as it directly influences the nature and extent of drug contact which can occur. It has been estimated that the BBB excludes 95% of all drugs from entering the brain from the blood.[1] The diffusion of compounds across the BBB is dependent on the physicochemical properties of the compounds, specifically lipid solubility, molecular weight, and electrical charge or ionization.[2,3] In addition to the BBB, there are a number of other factors that influence the concentration of drugs within the CNS. Drugs that are highly protein bound will have diminished capacity to traverse the BBB.[3,4] It is also well recognized that meningeal inflammation will increase the penetration of many drugs into the CNS. It is important to recognize that brain tissue concentrations and cerebrospinal fluid (CSF) concentrations may not be the same—that is, there is compartmentalization. For example, brain tissue concentration of chloramphenicol following treatment is nine times the plasma concentration, yet CSF chloramphenicol concentration is only about 50% of simultaneous plasma concentration.[4] Brain tissue and CSF concentrations of azithromycin differ markedly.[5] The elimination half-life for a drug in the CNS or CSF may differ markedly from that in serum and is frequently longer (allowing accumulation).[3] Finally, the mechanism of bulk flow will remove chemicals from the CSF independent of their physicochemical properties.

In addition to the passive mechanisms described above, there are some active mechanisms of the BBB which influence CNS drug concentrations. There is a low capacity facilitated diffusion system in the BBB for some penicillin and cephalosporin antimicrobials which transport these drugs from the blood into the extracellular fluid of the CNS.[6,7] In addition, there is also a mechanism for active efflux from the CSF for penicillins and other beta-lactam antimicrobials, macrolide antimicrobials, ivermectin, vinca alkaloids, digoxin, and dexamethasone, among others, using the multidrug resistance transporter protein in the BBB.[2,6] The activity or presence of this transporter in the horse has not been investigated (Table 4.1).

ANTIBACTERIAL DRUGS

There are few antibiotics used in the horse which readily achieve antibacterial concentrations in the CNS or CSF. Most information known about CSF antibiotic concentrations is extrapolated from humans and laboratory animals. As indicated above, a number of factors influence such concentrations, and direct extrapolation may not be accurate.

Penicillin achieves concentrations in the CSF that are roughly 10% of corresponding serum concentrations.[8] While meningeal inflammation does increase

Table 4.1. Factors that Influence Central Nervous System (CNS) Concentration of Drugs

Presence of BBB
Lipophilicity of compound
Protein binding
Physical size/radius
Molecular charge
Active transport
Active efflux
Bulk flow
Presence or absence of meningeal inflammation

the proportion of penicillin that can cross the BBB, this is variable, and may not be adequate to result in therapeutic concentrations. Ampicillin achieves higher concentrations within the CSF than penicillin, however only in the presence of meningeal inflammation.[9]

The third- and fourth-generation cephalosporins—ceftazidime, cefotaxime, and cefepime—achieve good CSF concentrations following peripheral administration and have favorable spectrum of activity. Compounds in the cephalosporin class do not uniformly cross the BBB, however. Proper dosages and dose intervals for many of these drugs have not been established in the horse at this time. Ceftriaxone has been investigated in the horse, and a single intravenous (IV) dose of 50 mg/kg resulted in a CSF concentration of 0.6 ± 0.14 μg/ml at 3 h after dosage and 0.4 ± 0.31 μg/ml at 8 h after dosage.[10] The CSF concentration of ceftriaxone varied markedly between horses being studied, and the authors concluded that the variability was due to the presence of mild inflammation induced by an indwelling intrathecal catheter. The CSF concentrations achieved exceed the minimum inhibitory concentration (MIC) for many equine pathogens, making ceftriaxone an attractive choice for the treatment of bacterial meningitis in horses. It was suggested that a dose of 25 mg/kg IV BID would be adequate; however, this was not investigated specifically. Owing to the cost, ceftriaxone may be limited to use in foals and small ponies. Based on pharmacokinetic studies in neonates, a dose of 25 mg/kg IV, every 12 h, was suggested for neonatal foals.[11] Cefotaxime has been used with success in foals with meningitis at a dose of 40 mg/kg QID.[12,13] Specific CSF concentrations resulting from the dosage were not reported. Cephapirin could not consistently be found in the CSF of horses following intramuscular dosages of 20 mg/kg, and it is not likely to be useful in the treatment of CNS infections in horses.[14] No ceftiofur could be detected in the CSF of mares following multiple doses of ceftiofur (2 mg/kg body weight).[15] Dosages for other cephalosporins must be extrapolated from those used in humans and may or may not be appropriate. The expense of these antibiotics limits their use to the neonate in many cases.

Chloramphenicol has been extensively evaluated in the horse, and it has been used for the treatment of a number of equine infectious conditions.[16] Chloramphenicol has a favorable spectrum of activity for equine pathogens, and in humans the CSF concentration achieves almost 60% of serum concentrations when administered orally.[17] CSF concentrations in horses are similar.[18] The half-life of chloramphenicol in the horse is short following IV administration (0.43 h)[19] and somewhat longer after multiple oral doses (3.8 h).[18] The metabolism and excretion of chloramphenicol in neonatal foals has been demonstrated to be similar to adult horses by 7 days of age.[16,20] This short half-life makes frequent dosing necessary and limits its intravenous use. Dose recommendations vary widely but are commonly reported as 25–59 mg/kg orally every 6 h.[21,22] The limitations on the use of chloramphenicol may make availability of this drug difficult in some circumstances.

Potentiated sulfonamide combinations—trimethoprim/sulfamethoxazole (TMP/SMZ) or ormetoprim/sulfadimethoxine (OMP/SDM)—are commonly used in the treatment of equine infections. At a dose of 2.5 mg/kg TMP and 12.5 mg/kg SMZ, CSF concentrations in one horse were 0.15 μg/ml TMP (28% of corresponding serum concentration) and 4.8 μg/ml SMZ (43% of corresponding serum concentration).[23] These concentrations were not adequate to be effective against a number of equine pathogens reported by the authors. Although the authors suggested that there was evidence of accumulation of SMZ in the CSF, this was not confirmed. Meningeal inflammation does not appear to enhance the CSF concentration of TMP/SMZ;[24,25] hence use of this drug in CNS infections of the horse should be considered carefully, and may not be optimum. The coadministration of intravenous dimethyl sulfoxide (DMSO) had no effect upon

CSF concentrations of TMP or SMZ.[26] Following dosing at 9.2 mg/kg OMP and 45.8 mg/kg SDM, OMP concentration in the CSF was 0.08 ± 0.056 μg/ml, and SDM concentration was 2.1 ± 0.77 μg/ml. This represents 47% (OMP) and 2.6% (SDM) of corresponding serum concentrations.[26] These concentrations are well below previously published MICs for a number of equine pathogens.[27,28] These values were derived from samples taken at only one time point and are not likely to constitute peak concentrations, however.

The use of sulfonamide drugs in the horse is known to be associated with a number of potential complications, including diarrhea and anemia. In addition, one report describes neurologic signs in four of six pony stallions following treatment with TMP/SMZ. Clinical signs noted were clumsy thrusts and weakness and unsteadiness when mounting. Formal neurologic evaluations were not performed, unfortunately, but these signs are consistent with spinal ataxia.[29] This observation has not been further investigated, and its significance is unclear at this time.

Fluoroquinolones are highly lipid soluble and have been reported to achieve high concentrations in the CNS following parenteral administration.[30] In dogs treated with enoxacin, good CSF concentrations were reported, and concentrations of pefloxacin in healthy dogs resulted in CSF concentrations that were 55% of those in serum.[31] The most commonly used fluoroquinolone in horses is enrofloxacin, and the CSF concentration was approximately 15 and 25% of corresponding serum concentrations at 74 and 84 h following treatment.[32] The concentration achieved at a dosage of 5 mg/kg BID PO exceeded the MIC for most equine pathogens (0.5 μg/ml).[32] This drug would be a valuable compound in the treatment of bacterial meningitis; however its use in foals is associated with a high risk of arthropathy, severely limiting its use in young foals. Very high doses of enrofloxacin (25 mg/kg IV) as a bolus dose have resulted in seizures in horses.[33] Giving the dose diluted or more slowly ameliorated the effect. This is assumed to result from transient high CSF concentrations and the binding of γ-aminobutyric acid (GABA) receptors in the CNS.

Rifampin achieves high CSF concentrations; however, it must be administered concurrently with other antibiotics due to the rapid development of resistance.[34] Specific investigations in the horse are not reported. Metronidazole is highly lipophilic, and it achieves high concentrations in the CSF of many species.[35,36] Metronidazole is almost exclusively useful for anaerobic infections, which have not been reported in the CNS of the horse; hence its value is limited.

Parenteral administration of aminoglycoside antimicrobials does not result in measurable concentrations within the CNS.[22,37] Administration of doxycycline at 10 mg/kg body weight did not result in measurable concentrations of the drug within the CSF of horses.[38] Entry of erythromycin into the CNS and CSF is considered poor.[3] Treatment of humans with conventional doses of azithromycin has been found to result in high CNS tissue concentrations (up to 3.6 ± 3.81 μg/g tissue) which were 10 times the serum concentration.[5] Corresponding CSF azithromycin concentrations were minimal to undetectable.[5] Corresponding studies have not been performed in horses, but would suggest that azithromycin may have value in the treatment of CNS abscesses caused by sensitive organisms (Table 4.2).

The optimal antimicrobial to use in equine CNS infections has not been established and must be determined based on culture and sensitivity of the organism, as well as knowledge of the pharmacology of the drug and its ability to enter the CNS and achieve an adequate concentration. It is unclear whether higher doses and longer intervals, or more frequent administration, are most important in antimicrobial treatment of CNS infections.[3] In one study describing the treatment of human meningitis,

Table 4.2. Relative Drug Concentrations in Cerebrospinal Fluid Following Parenteral Dosing

Good	Poor
Ceftriaxone	Penicillin
Cefotaxime	Ampicillin
Chloramphenicol	Cephapirin
Rifampin	Ceftiofur
TMS/SMZ*	Doxycycline
OMP/S*	
Metronidazole	

*Marginal.

antimicrobial combinations were most commonly used, including one or more third-generation cephalosporins, penicillin, ampicillin, and chloramphenicol.[3] It is reasonable to assume that due to the limited penetration of most antibiotics into the CSF of horse, combination therapy would be of value. This must be determined on a case-by-case basis accompanied by culture and sensitivity data.

One means to achieve high CSF concentrations of antibiotics is by direct injection into the CSF (intrathecal administration). Intrathecal treatment can be considered in cases in which the recovered organism is sensitive only to drugs that have poor penetration of the BBB. This method of treatment has been utilized in humans, particularly when treating resistant organisms, and high concentrations of antibiotics result.[39,40] In humans, 5 mg of gentamicin intraventricularly, once per day, has been recommended.[3] No reports using intrathecal antibiotics in horses could be found, and the dose and frequency of treatment are totally unknown. Anecdotally, seizures have been reported in horses from this procedure, likely associated with the carrier and formulation of the compounds used.

ANTIVIRAL DRUGS

Few antiviral drugs are available for use in the horse; however, acyclovir has been proposed for the treatment of equine herpesvirus-1 (EHV-1) myeloencephalopathy.[41] Acyclovir is an acyclic nucleoside analogue which has a good activity against herpes simplex virus type 1 and 2. Acyclovir has been shown to inhibit the replication of EHV-1 in Syrian hamsters at a dose of 100 mg/kg.[42] *In vitro* evaluation of the effectiveness of acyclovir against EHV-1 isolates has been performed, and good activity was demonstrated against some strains, although significant strain variation in susceptibility was demonstrated.[43] Oral availability of acyclovir is poor, and plasma concentrations after dosing with 20 mg/kg were below the limits of detection of the assay (<0.15 μg/ml).[41] This is in contrast to another report in which multiple doses of the drug (10 mg/kg) resulted in plasma concentrations of 0.2–0.38 μg/ml.[43] These concentrations were effective for some, but not all EHV-1 isolates *in vitro*.[43] Acyclovir has been used clinically at a dose of 20 mg/kg q 8 h in one EHV-1 myeloencephalitis outbreak, but a clear benefit was not demonstrated.[44] Current evidence does not support the use of acyclovir in horses with EHV-1-associated disease.

ANTI-INFLAMMATORY DRUGS

The CNS is considered an "immune privileged site," in that response to infection of the CNS is less robust than that noted in other tissues. This restriction upon the degree of inflammation likely has survival benefit. In the treatment of CNS infections, therefore, control of inflammation is of paramount importance. Control of inflammation is credited with improving outcomes in cases of human bacterial meningitis. Prostaglandins and thromboxans are produced in the CNS in a number of clinical conditions, including seizures, inflammation, traumatic brain injury, and cerebral vascular disease.[45] The relative concentrations of and ability to generate eicosenoids appear to vary depending upon the region of the CNS affected, however.[45] While this topic has not been evaluated in the horse, it is presumed that a similar increase in prostanoid products would be found. From the preceding observations, a number of nonsteroidal anti-inflammatory drugs (NSAIDs) have been recommended in neuroinflammatory disease.

The NSAIDs ibuprofen, aspirin, and indomethacin increase survival in mice with Sandhoff's disease, an inflammatory neurodegenerative disorder.[46] These findings suggest that the NSAIDs should be useful in horses with neuroinflammation, as well as attenuating fever, myalgia, and perhaps improving appetite. No recommendations can be made at this time, however, in regard to the specific NSAID to use, or appropriate dosages. These should be determined on a case-by-case basis.

The use of corticosteroids in horses with neuroinflammation is controversial, as it is in people. It is well recognized that corticosteroids are effective in the treatment of cerebral edema, and that they attenuate tissue injury by inhibiting host mediators at several steps in the inflammatory process.[47] Concern has been expressed regarding the potential for the immunosuppression associated with dexamethasone usage, allowing infection to progress. There is little to no empiric support of this concept, however. Extensive research has been conducted regarding the effects of steroids in CNS infections in humans and laboratory animals. In one study of bacterial meningitis in adults, treatment with dexamethasone was found to reduce the relative risk of death (0.48, 95% CI 0.24–0.96, $P = 0.04$) when compared to no steroids,[48] while another study found that the use of corticosteroids in human patients with bacterial

meningitis reduced death, hearing loss, and neurologic sequelae.[49] A meta-analysis of randomized clinical trials also found that treatment with dexamethasone in people was beneficial and associated with low risk of side effects.[50] No comparable studies are reported in horses; however, it is assumed that the general beneficial effects upon cerebral inflammation would also exist. In horses, the risk of laminitis associated with corticosteroid use must be considered and assessed on an individual case basis; however a short-term course of corticosteroids in horses with bacterial meningitis seems warranted.

The use of corticosteroids in viral disease is also controversial; however, corticosteroids have been used successfully in people with West Nile Virus encephalitis[51] and have been proven beneficial in acute viral meningitis.[52] Furthermore, glucocorticoids have been found to be beneficial in people and experimental animals with herpes simplex encephalitis, and the use of glucocorticoids did not result in an increased viral load.[53] In fact, in another study, the use of corticosteroids alone was associated with a reduction in viral load by 63% ± 13%.[54] Similar studies have not been reported for horses with viral encephalitis; however, these studies provide compelling evidence for the value of corticosteroids in horses with viral induced neuroinflammation. In horses with neurologic deficits due to viral encephalitis, which are severe enough to require hospitalization, a short course of corticosteroids is strongly indicated.

Another commonly used anti-inflammatory drug in horses is dimethylsulfoxide (DMSO). It is commonly recommended for treatment of horses with neuroinflammation; however, there is little evaluation of its use in the horse. Clinical experience suggests that it does have an anti-inflammatory effect, but this is difficult to establish conclusively. There is, however, a large body of work describing the effects of DMSO in neurologic disease in laboratory animal species, as well as its clinical use in humans. Calcium flux as a result of excitotoxic amine release is a well-recognized cause of neuronal cell death. It has been demonstrated that DMSO at concentrations that are associated with clinical treatment decrease excitotoxic cell death of neurons.[55] Further, DMSO has been shown to enhance the drug-induced blockade of calcium channels.[56] Intravenous DMSO at 1 mg/kg body weight, given as a 10% solution, has been shown to decrease intracranial pressure (ICP) by 45% in a model of brain edema in rabbits.[57] In addition, DMSO reduced neuronal cell death in an *in vivo* model of ischemia-reperfusion,[58] rapidly decreased ICP in human patients suffering head trauma, and improved cerebral perfusion pressure and neurologic outcomes.[59] It is expected that horses would have a similar response to DMSO, and a dose of 0.5–1 g/kg as a 10% solution (IV), two times per day, is recommended in suspected cases of neuroinflammation. The drug should not be given at greater than a 20% solution, as hemolysis can be seen at concentrations greater than 20%. Dosages of 4 g/kg IV were associated with toxic signs in three of six treated horses. Signs included muscle trembling, loose stool, and colic, and abated quickly after cessation of the drug infusion.[60]

Other compounds used to combat CNS edema include mannitol and hypertonic saline. Both compounds are considered to reduce cerebral edema primarily due to their hyperosmolar effects, but some evidence suggests slightly different mechanisms to the reduction of ICP.[61] Various concentrations of hypertonic saline have been investigated in cases of brain edema, with improvement noted in ICP following treatment with as low as 1.8% NaCl.[62] The beneficial effects of hypertonic saline persist even when followed by normal crystalloid solutions[63] and appear to be due to its ability to draw water from the cell, decreasing tissue pressure.[63] The recommended dose of hypertonic saline for horses with head trauma is 4–6 ml/kg of 5 or 7% NaCl as a bolus, which can then be followed by normal crystalloid solutions at a maintenance dose.[64] Isotonic fluids should not be given to horses with head trauma at high dose rates, such as that used for circulatory shock, as this is likely to increase cerebral edema and ICP.[65]

Mannitol is a hyperosmolar solution that has been used to reduce ICP. Mannitol is a 6-carbon nonmetabolizable polyalchohol with a molecular weight of 182.[66] Several theories have been proposed to explain the effects of mannitol on ICP. The osmotic theory has the most support and states that the CNS shrinkage is a result of osmotically driven movement of fluid from the tissue into the vascular component. A variety of studies have confirmed that mannitol reduces water content of tissue (e.g., brain).[61] Additional experimental work, however, has suggested that additional mechanisms may be involved in the reduction of ICP associated with mannitol. These

theories include a reduction of CSF production, as well as direct vascular effects.[67,68] It is likely that a combination of osmotic and other effects is present.

Dosages of mannitol of 1–2 g/kg body weight, intravenously two to four times per day, have been suggested for horses with suspected cerebral edema.[69] Rapid reduction of ICP is noted in experimental animals following bolus dosing of mannitol. A rebound effect may occur after treatment is stopped, and repeated dosing in experimental animals has led to progressively reduced effects associated with accumulation of mannitol in tissues.[61,70] Mannitol should not be used in horses in which subarachnoid or intraparenchymal hemorrhage is present, due to the potential to exacerbate bleeding or increase ICP.

REFERENCES

1. Pardrige WM. 1999. Non-invasive drug delivery to the human brain using endogenous blood–brain barrier transport systems. *PSTT* 2:49–59.
2. de Vries HE, Kuiper J, De Boer AG, *et al*. 1997. The blood–brain barrier in neuroinflammatory disease. *Pharmacol Rev* 49:143–55.
3. Nau R, Sorge F, Prange H. 1998. Pharmacokinetic optimisation of the treatment of bacterial central nervous system infections. *Clin Pharmacokinet* 35:223–46.
4. Brewer BD. 1984. Therapeutic strategies involving antimicrobial treatment of the central nervous system in large animals. *J Am Vet Med Assoc* 185:1217–21.
5. Jaruratanasirikul S, Hortiwakul R, Tantisarasart T, *et al*. 1996. Distribution of azithromycin into brain tissue, cerebrospinal fluid, and aqueous humor of the eye. *Antimicrob Agents Chemother* 40:825–6.
6. Spector R. 1986. Ceftriaxone pharmacokinetics in the central nervous system. *J Pharmacol Exp Ther* 236:380–3.
7. Spector R. 1990. Advances in understanding the pharmacology of agents used to treat bacterial meningitis *Pharmacology* 41:113–8.
8. Barling R. 1978. The penetration of antibiotics into cerebrospinal fluid and brain tissue. *J Antimicrob Chemother* 4:203–27.
9. Thea D. 1989. Use of antibacterial agents in infections of the central nervous system. *Infect Dis Clin North Am* 3:553–70.
10. Ringger NC, Pearson EG, Gronwall R, *et al*. 1996. Pharmacokinetics of ceftriaxone in healthy horses. *Equine Vet J* 28:476–9.
11. Ringger NC, Brown MP, Kohlep SJ, *et al*. 1998. Pharmacokinetics of ceftriaxone in neonatal foals. *Equine Vet J* 30:163–5.
12. Morris DD, Rutkowski J, Kent Lloyd KC. 1987. Therapy in two cases of neonatal foal septicemia and menigitis with cefotaxime. *Equine Vet J* 19:151–4.
13. Gardner SY, Sweeney RW, Divers TJ. 1993. Pharmacokinetics of cefotaxime in neonatal pony foals. *Am J Vet Res* 54:576–9.
14. Brown MP, Gronwall RR, Houston AE. 1986. Pharmacokinetic and body fluid and endometrial concentrations of cephapirin in mares. *Am J Vet Res* 47:784–8.
15. Cervantes CC, Brown MP, Gronawall R, *et al*. 1993. Pharmacokinetics and concentrations of ceftiofur sodium in body fluids and endometrium after repeated intramuscular injections in mares. *Am J Vet Res* 54:573–5.
16. Page S. 1991. Chloramphenicol 3: Clinical pharamacology of systemic use in the horse. *Aust Vet J* 68:5–8.
17. Friedman C. 1979. Chloramphenicol disposition in infants and children. *J Pediatr* 95:1071–7.
18. Gronwall R, Brown MP, Merritt AM, *et al.* 1986. Body fluid concentrations and pharmacokinetics of chloramphenicol given to mares intravenously or by repeated gavage. *Am J Vet Res* 47:2591–5.
19. Brown MP, Kelly RH, Gronwall RR, *et al*. 1984. Chloramphenicol sodium succinate in the horse: Serum, synovial, peritoneal, and urine concentrations after single-dose intravenous administration. *Am J Vet Res* 45:578–80.
20. Brumbaugh GW, Martens RJ, Knight HD, *et al*. 1983. Pharmacokinetics of chloramphenicol in the neonatal horse. *J Vet Pharmacol Ther* 6:219–27.
21. Knight HD. 1975. Antimicrobial agents used in the horse. *Proc Annu Meeting Am Assoc Equine Pract* 21:131–45.
22. Dowling PM. 2004. Antimicrobial therapy. In *Equine Clinical Pharmacology*, edited by Bertone JJ, Horspool LJI, 13–48. Philadelphia, PA:Saunders Co.
23. Brown MP, Gronwall R, Castro L. 1988. Pharmacokinetics and body fluid and endometrial concentrations of trimethoprim–sulfamethoxazole in mares. *Am J Vet Res* 49:918–22.
24. Levitz R, Quintaliani R. 1984. Trimethoprim-sulfamethoxazole for bacterial meningitis. *Ann Int Med* 100:881–90.
25. Dudley M, Levitz R, Quintaliani R, *et al*. 1984. Pharmacokinetics of trimethoprim-sulfamethoxazole in serum and cerebrospinal fluid of adult patients with normal meninges. *Antimicrob Agents Chemother* 26:811–4.
26. Green SL, Mayhew IG, Brown MP, *et al*. 1990. Concentrations of trimethoprim and sulfamethoxazole

in cerebrospinal fluid and serum in mares with and without a dimethyl sulfoxide pretreatment. *Can J Vet Res* 54:215–22.
27. Brown MP, Gronwall RR, Houston AE. 1989. Pharmacokinetics and body fluid and endometrial concentrations of ormetoprim-sulfadimethoxine in mares. *Can J Vet Res* 53:12–6.
28. Adamson PJW, Wilson WD, Hirsch DC, *et al*. 1985. Susceptibility of equine bacterial isolates to antimicrobial agents. *Am J Vet Res* 46:447–50.
29. Bedford SJ, McDonnell SM. 1999. Measurements of reproductive function in stallions treated with trimethoprim–sulfamethoxazole and pyrimethamine. *J Am Vet Med Assoc* 215:1317–9.
30. Cottagnoud P, Tauber M. 2003. Fluoroquinolones in the treatment of meningitis. *Curr Infect Dis Rep* 5:329–36.
31. Neer T. 1988. Clinical pharmacologic features of fluoroquinolone antimicrobial drugs. *J Am Vet Med Assoc* 193:577–80.
32. Giguere S, Sweeney RW, Belanger M. 1996. Pharmacokinetics of enrofloxacin in adult horses and concentration of the drug in serum, body fluids, and endometrial tissues after repeated intragastrically administered doses. *Am J Vet Res* 57: 1025–30.
33. Bertone AL, Tremaine WH, Macoris DG, *et al*. 2000. Effect of long-term administration of an injectable enrofloxacin solution on physical and musculoskeletal variables in adult horses. *J Am Vet Med Assoc* 217:1514–21.
34. Farr M. 1982. Rifampin. *Med Clin North Am* 66: 157–68.
35. Anon. 2004. Metronidazole. In *AHFS Drug Information*, edited by McEvoy G, 848–57. Bethesda, MD:American Society of Health System Pharmacists.
36. Dowling PM. 1999. Clinical pharmacology of nervous system disease. *Vet Clin North Am Equine Pract* 15:575–88.
37. Neuwelt EA, Baker DE, Pagel MA, *et al*. 1984. Cerebrovascular permeability and delivery of gentamicin to normal brain and experimental brain abscess in rats. *Neurosurgery* 61:430–9.
38. Bryant J, Brown MP, Gronwall R, *et al*. 2000. Study of intragastric administration of doxycycline: pharmacokinetics including body fluid, endometrial and minimum inhibitory concentrations. *Equine Vet J* 32:233–8.
39. Corpus K, Weber K, Zimmerman C. 2004. Intrathecal amikacin for the treatment of pseudomonal meningitis. *Ann Pharmacother* 38:992–5.
40. Matasubara H, Makimoto A, Higa T, *et al*. 2003. Successful treatment of meningoencephalitis caused by methicillin-resistant *Staphylococcus aureus* with intrathecal vancomycin in an allogenic peripheral blood stem cell transplant recipient. *Bone Marrow Transplant* 31:65–7.
41. Wilkins P, Papich M, Sweeney RW. 2005. Pharmacokinetics of acyclovir in adult horses. *J Vet Emerg Crit Care* 15:174–8.
42. Rollinson R, White G. 1983. Relative activities of acyclovir and BW 759 against Aujeskys disease and equine rhinopneumonitis viruses. *Antimicrob Agents Chemother* 24:221–6.
43. Wilkins P. 2004. Acyclovir in the treatment of EHV-1 myeloencephalopathy. *Proc 22nd Annu Meeting ACVIM* 170–2.
44. Friday PA, Scarratt WK, Elvinger F, *et al*. 2000. Ataxia and paresis with equine herpesvirus type 1 infection in a herd of riding school horses. *J Vet Intern Med* 14:197–201.
45. Wolfe L, Horrocks L. 1994. Eicosenoids. In *Basic Neurochemistry*, edited by Siegel C, 475–90. New York, NY:Raven Press.
46. Jeyakumar M, Smith D, Williams I, *et al*. 2004. NSAIDs increase survival in the Sandhoff disease: synergy with N-butyldeoxynorimycin. *Ann Neurol* 56:642–9.
47. Jafari H, McCracken G. 1994. Dexamethasone therapy in bacterial meningitis. *Pediatr Ann* 23:82–8.
48. de Gans J, van de Beek D. 2002. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 347:1549–56.
49. Morris A. 2004. Review: adjuvant corticosteroid therapy reduces death, hearing loss, and neurologic sequelae in bacterial meningitis. *Evid Based Med* 9:48.
50. McIntyre P, Berkey C, King S, *et al*. 1997. Dexamethasone as adjunctive treatment in bacterial meningitis. A meta- analysis of randomized clinical trials since 1988. *JAMA* 278:925–31.
51. Pyrgos V, Younus F. 2004. High dose steroids in the management of acute flaccid paralysis due to West Nile virus infection. *Scand J Infect Dis* 36:509–12.
52. Nakano A, Yamasaki R, Miyazaki S, *et al*. 2003. Beneficial effect of steroid pulse therapy on acute viral encephalitis. *Eur Neurol* 50:225–9.
53. Meyding-Lamade U, Oberlinner C, Seyfer S, *et al*. 2003. Experimental herpes simplex virus encephalitis: a combination therapy of acyclovir and glucocorticoids reduces long-term magnetic resonance imaging abnormalities. *J Neurovirol* 6:118–25.
54. Thompson K, Blessing W, Wesselingh S. 2000. Herpes simplex replication and dissemination is not increased by corticosteroid treatment in a rat model of focal herpes encephalitis. *J Neurovirol* 6:25–32.

55. Lu C, Mattson M. 2001. Dimethyl sulfoxide suppresses NMDA and AMPA-induced ion currents and calcium influx and protects against excitotoxic death in hippocampal neurons. *Exp Neurol* 170: 180–5.
56. Wu L, Karpinski E, Wang R, *et al*. 1992. Modification by solvents of the action of nifedipine on calcium channel currents in neuroblastoma cells. *Naunyn Schmiedebergs Arch Pharmacol* 345: 478–84.
57. James H, Camp P, Harbaugh R, *et al*. 1982. Comparison of the effects of DMSO and pentobarbitone on experimental brain oedema. *Acta Neurochir* 60:245–55.
58. Phillis JN, Estevez AZ, O'Regan MH. 1998. Protective effects of the free radical scavengers dimethyl sulfoxide and ethanol, in cerebral ischemia in gerbils. *Neurosci Lett* 244:109–11.
59. Karaca M, Bilgin U, Akar M, *et al*. 1991. Dimethyl sulfoxide lowers ICP after closed head trauma. *Eur J Pharmacol* 40:113–4.
60. Appell L, Blythe L, Lassen E, *et al*. 1992. Adverse effects of rapid intravenous DMSO administration in horses. *J Equine Vet Sci* 12:215–8.
61. Berger S, Schurer L, Hartl R, *et al*. 1995. Reduction of post-traumatic intracranial hypertension by hypertonic/hyperoncotic saline/dextran and hypertonic mannitol. *Neurosurgery* 37:98–108.
62. Shackford S, Zhuang J, Schmoker J. 1992. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. *J Neurosurg* 76:91–8.
63. Gunner W, Jonasson O, Nerkittuem G. 1988. Head injury and hemorrhagic shock: Studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution and dextran-40. *Surgery* 103: 398–402.
64. Bertone JJ. 1991. Hypertonic saline in the management of shock in horses. *Compend Contin Educ Pract Vet* 13:665–70.
65. Crowe D. 1992. Triage and trauma management. In *Veterinary Emergency and Critical Care Medicine*, edited by Murtaugh R, Kaplan P, 77. St. Louis Mosby Year Book.
66. Kochevar DT. 2001. Diuretics. In *Veterinary Pharmacology and Therapeutics*, edited by Adams HR, 534–52. Ames, IA:Iowa State University Press.
67. Hartwell RC, Sutton LN. 1993. Mannitol, intracranial pressure, and vasogenic edema. *Neurosurgery* 32: 444–50.
68. Shapira Y, Artru A, Donato T, *et al*. 1992. Effect of mannitol on cerebrospinal fluid dynamics and brain edema. *Anesthesiology* 77:A782.
69. Matthews H. 1998. Spinal cord, vertebral, and intracranial trauma. In *Equine Internal Medicine*, edited by Reed SM, Bayly W, 457–66. Philadelphia, PA:W.B.Saunders.
70. Kauffman AM, Cardoso ER. 1992. Aggravation of vasogenic cerebral edema by multiple dose mannitol. *J Neurosurg* 77:584–9.

Section II:
Clinical Equine Neurology

5
Neurologic Examination

Martin Furr and Stephen Reed

Many veterinarians feel that the evaluation of neurologic disease is a complicated and difficult procedure. In fact, the neurologic examination is straightforward and relatively simple; interpretation requires knowledge of equine neurologic disorders, as well as a basic understanding of equine neuroanatomy. The key to a successful neurologic examination is to do the examination in a consistent and organized fashion. It is important to develop a routine, then do it the same way each time. This approach ensures that some parts of the examination are not forgotten. In addition, it increases the consistency of the exam, as many horses performing the same maneuver are seen. A standardized examination form is a valuable aid in this and can be concise.

The goals of the neurologic examination are to determine whether disease of the nervous system exists, to localize the lesion to a particular area of the nervous system, and to describe and record the responses as a baseline for future evaluations. In addition, repeated examinations over time may provide information that is useful in the diagnosis of various disorders. This "severity vs. time" information finds acute onset in horses with trauma or infection, a slowly progressive course in horses with equine protozoal myeloencephalitis (EPM) or EDEM, and a chronic fluctuating course in horses with cervical compression.

It is also important to recognize that the neurologic examination should not take place "in a vacuum"—it is only one part of a complete physical examination and will be used in concert with the other physical examination findings to reach a final conclusion about the horse. Signalment and history are also important and should never be overlooked.

The specific order of examination is not of particular importance; however a "nose-to-tail" approach is employed by most clinicians as being the most convenient. The evaluation is begun by a general observation of the horse, including its attitude and alertness, head and body position, position of the limbs, and symmetry of muscle development. The horse should be alert and should respond to the examiner and its environment. The horse should be observed at this time for any unusual behavior, presence of a head tilt, yawning, or muscle fasciculations. Subtle abnormalities are more easily seen when the horse is relaxed and may be hidden once the horse is handled. The horse's general posture and body position should be noted. The limbs should be evenly and squarely placed under the horse at each "corner of the horses body"—abnormal limb position should alert the examiner to potential deficits of proprioception. If suspected, the presence of proprioceptive deficits should be further evaluated during the gait analysis.

The components of the neurologic examination include the cranial nerve examination; limb and placing responses; gait analysis; and tail, anal, and panniculus reflexes.

CRANIAL NERVES

The tests listed in Figure 5.1 and Table 5.1 are sufficient to provide a complete evaluation of the cranial nerves and can be quickly performed during a routine physical examination. Changes in mentation or behavior can be difficult for the clinician to assess but are aided by careful observation and input from the owner or caretaker about the horse's normal behavior and any changes that may have occurred.

Neurologic Examination

Owner: _____ Horse: _____
Behavior/Mentation: _____
Head/Neck posture: _____

	Left	Right
Vision		
Menace		
Pupil/PLR		
Horners		
Strabismus		
Facial sens		
Facial symmetry		
Nystagmus: Resting Positional		
Head tilt		
Swallow/voice	Norm	Abnorm
Slap test	Norm	Abnorm
Tongue tone	Norm	Abnorm

Grade 0- No deficits
Grade 1- Just detected at a normal gait, but worsened by backing, turning, loin pressure or neck extension
Grade 2- Deficit easily detected at normal gait and exaggerated by backing, turning, swaying, loin pressure and neck extension
Grade 3- Deficit very prominent on walking, with a tendency to buckle or fall with backing, turning, loin pressure, or neck extension
Grade 4- Stumbling, tripping and falling spontaneously
Grade 5- Horse recumbent

Gait Assessment (0–5 as above)

	Thoracic		Pelvic	
	Left	Right	Left	Right
Paresis				
Ataxia				
Spasticity				
Dysmetria				

Neck and forelimbs	L	R	**Hindlimbs**	L	R	**Tail and Anus**	L	R
Muscle mass			Muscle mass			Muscle tone		
Sensation			Sensation			Sensation		
Hop			Placing			Reflexes		
Placing			Strength			Strength		

(Normal = 2; Decreased=1, Exaggerated = 3, Absent = 0)

Comments:_____

Date:_____ Examiner:_____

Figure 5.1. An example of a neurologic examination form.

Behavioral changes may be intermittent or continuous. Adoption of abnormal postures and head pressing, however, are readily noted and are clear signs of cerebral disease. Head pressing or compulsive walking suggests diffuse encephalopathy, while circling is associated with asymmetric forebrain lesions. Assessment of the state of consciousness is recorded in a decreasing continuum as alert, depressed, stuporus, semicomatose, or comatose. Horses that are depressed react to their environment

Table 5.1. Tests of Cranial Nerve Function

Test	Nerve Tested	Abnormal Response/Interpretation
Menace	Optic, Facial	No eye blink; blindness. Must differentiate blindness from facial nerve dysfunction
Pupillary light response	Optic, Oculomotor	No response to bright light directed in eye
Horner's syndrome	Cervical sympathetic	Sweating around base of ear and eye, ptosis
Facial sensation	Facial (sensory)	Failure to respond to stimulation of facial skin
Facial symmetry	Facial (motor)	Asymmetry of muzzle, +/− ear droop, food impacted in cheek
Palpebral reflex	Trigeminal, Facial (motor)	Failure to blink
Nystagmus	Oculomotor, vestibular system	Central lesions associated with positional nystagmus; peripheral lesions are non-positional
Swallow	Glossopharyngeal, Vagus	Inability to swallow as determined by observation or passing of stomach tube
Tongue tone	Hypoglossal	Failure to withdraw tongue, or tongue weak when pulled

or stimulation in an inappropriate or diminished manner. Stupor describes a horse that appears asleep, yet responds to sound, light, or noxious stimuli. Semicoma is a state of partial responsiveness to stimuli and coma is a state of complete unresponsiveness to stimuli. The determination of state of consciousness is made by observation and response to noxious stimuli such as a skin pinch.

The position and coordination of the head should be examined while the horse is at rest and relaxed. The head should be symmetrical and held straight upright when viewed from the front. Head posture and coordination are controlled by the cerebellar and vestibular regions of the central nervous system (CNS) in response to sensory input from the head, limbs, and trunk. Smooth coordination of head movements are controlled by the cerebellum, and cerebellar disease results in jerky, bobbing movements of the head which are made worse when the horse attempts to prehend food. Lateral deviation of the head and neck should be differentiated from a head tilt. Lateral deviation of the head suggests asymmetrical forebrain disease, cervical soft tissue or bone disease, or spinocerebellar degeneration. When viewed from the side, the horse's head should be held higher than the withers; a lower resting position is seen in diseases causing diffuse neuromuscular weakness (e.g., botulism) or cervical pain. The willingness of the horse to flex its neck should be determined by offering grain or grass and slowly withdrawing it to the point of the shoulder. Normal horses will follow the offered feed easily by lateral flexion of the neck. Horses with neck pain will either resist turning the neck and back up, or turn the head on its side and flex at the poll to reach the feed.

Olfaction is not routinely tested, and vision is assessed by observation of the horse's movements in an unfamiliar environment, or failure to demonstrate a menace response. It should be noted, however, that cerebellar disease can result in a loss of the menace response in a visual horse. Other signs of cerebellar disease (such as intention tremors or hypermetric gait) should be present if this is the cause of the altered menace response. The menace response can be difficult to elicit in some circumstances and should be repeated several times if questionable. Pupil size, position, and symmetry should be evaluated and also the direct and consensual pupillary light response evaluated. In normalcy, a bright light directed into one eye should result in

constriction of both the ipsilateral eye, as well as the contralateral eye (consensual response). Observation of the consensual response is often difficult for one examiner to perform in large animals; hence the "swinging-light" test has been described.[1] From a distance of about 18 inch, the light is shown alternately into each eye, and the more powerful, direct papillary light response is seen as the beam reaches it. It has been stated that most unilateral afferent pathway lesions in the eye, optic nerve, optic chiasma, or tract to the level of the midbrain will allow an ipsilateral dilation of the pupil to occur when light reaches the affected eye. This method takes advantage of the fact that the ipsilateral papillary light response is more powerful than the contralateral (consensual) response. The pathway for this response involves the optic nerve and chiasma, then through the optic tracts in the midbrain to the oculomotor nuclei. The motor pathway arises from these nuclei, traveling via the oculomotor nerve to the ciliary ganglia, then to the pupillary constrictor muscles. The nerve tracts for the papillary light response are within the brainstem and are not affected by lesions of the visual cortex. A widely dilated pupil in a visual eye suggests oculomotor nerve damage—there will be no direct or consensual light response.

The oculomotor nerve also innervates the extraocular muscles of the eye, along with the trochlear (CN4) and abducens nerves (CN6), controlling eye position. These nerves are tested by observation of eye position and motion, and abnormalities of the nerves result in an abnormal eye position (strabismus). When the nose is elevated, the eyes should move ventrally to maintain a horizontal gaze (the "Dolls eye" reflex). When the head is moved from side to side, the eyes should move slowly opposite the direction of the movement of the head, then move quickly in the direction of the head movement. This is referred to as a "normal vestibular" nystagmus, and its presence suggests an intact vestibular system, as well as normal function of CN3 (Oculomotor N), and CN4 (Trochlear N) and 6 (Abducens N). Spontaneous or positional nystagmus are always abnormal. Intact sympathetic innervation to the eye is evaluated by observation for Horner's syndrome. In this condition, disruption of sympathetic innervation results in pupillary constriction, ptosis of the upper eyelid, and protrusion of the nictitating membrane. Sweating of the cranial neck extending to the base of the ear is also associated. Mechanical deviations of the eye due to trauma, swelling, or periorbital disease may also occur and should be considered.

The head should be examined for facial symmetry, reflecting function of CN7 (Facial N), and facial sensation, which is solely mediated by CN5 (Trigeminal N). The motor branch of CN5 is evaluated by observation of the ability to chew, as well as evaluation of the masseter and temporal muscles, which will atrophy if CN5 is damaged. The head should also be examined for a head tilt, in which the poll is deviated toward the affected side. This reflects dysfunction of the vestibular system, which may be centrally or peripherally located. Central vestibular disease results in a nystagmus which varies with different head positions ("positional nystagmus"), while peripheral vestibular disease is non-positional.

Swallowing is mediated by input from both the glossopharyngeal nerve (CN9) and the vagus (CN10). Swallowing can be evaluated by observation of normal mastication and swallowing, the "gag" reflex, or by passing a stomach tube. Pharyngeal function and the swallowing reflex can also be tested by observation with an endoscope. With the endoscope positioned in the pharynx, the wall of the pharynx and arytenoid cartilages can be touched with a probe and swallowing is observed. The horse may be unable to swallow, or may swallow weakly, resulting in a dorsally displaced soft palate which they are then unable to reduce. Stertorous breathing may be found in horses with bilateral pharyngeal or laryngeal paralysis.

Additional means to evaluate pharyngeal/laryngeal function include the "slap test" (laryngeal adductory test).[2] In this test, the larynx is observed with an endoscope as the saddle area is slapped three to four times with moderate intensity. A normal response is an adductory flick of the contralateral arytenoid cartilage. Overstimulation results in a blunted laryngeal adductory response. Failure to demonstrate adductory laryngeal response after the slap test has been associated with cervical spinal cord lesions in a high percentage of cases.[2] In another report, however, the slap test was found to have a low sensitivity (50–58%) and a specificity of 69–75%.[3] The test is difficult to interpret in young animals or horses with laryngeal hemiplegia. If an endoscope is not available, then the larynx can be palpated to detect contraction following the slap.

This is less sensitive than the endoscopic method, however.

Tongue tone is dependent upon the function of the hypoglossal nerve (CN12) and can be tested by grasping the tongue and applying gentle traction. Inability to resist or withdraw the tongue suggests hypoglossal nerve damage. Atrophy of the tongue has also been described secondary to hypoglossal nerve injury.

The cervical reflexes should be examined. The cervicoauricular reflex (also called cervicofacial) is elicited by lightly tapping the skin between the jugular groove and the crest at the level of C2. A positive response is for the horse to flick the ear forward. Other authors have also reported a pulling back of the lips ("smile" reflex) as well as the local muscle contraction and ear movement.[1,4] An additional cervical reflex is the "local cervical" reflex noted between C3 and C6. Tapping the skin in the area between the crest and the jugular groove will result in local muscle contraction. This response is not as vigorous as the panniculus response over the trunk. Abnormalities of these reflexes have been noted in horses with cervical spinal cord disease.[5] Peripheral neuropathy due to arthritic compression of spinal nerves will also lead to an abnormal response.

The tail carriage and anal tone and reflex should be examined. Normal tail carriage is straight down, with normal movement in all directions. Most normal horses will clamp the tail if it is grasped and raised. Stimulation of the anus should result in a strong tail clamp and perhaps a "squatting" position. Abnormalities of tail strength and anal reflex may be seen in horses with botulism or inflammation of the cauda equina. Elevated tail carriage is commonly seen in horses with equine lower motor neuron (LMN) disease.

LIMB PLACEMENT AND PANNICULUS TESTS

These tests can be quickly performed and have value in detecting muscular weakness and conscious proprioceptive deficits. Abnormal limb positions, particularly a base-wide stance in the front limbs, may also be associated with vestibular disease. Limb placement tests are easier to perform and interpret on the front limbs. Typically, one front hoof is lifted, then placed across the other front leg. Horses should quickly move the hoof back into normal position, or resist placement into an abnormal position. An abnormal response is to leave the hoof in this crossed position for a prolonged period (usually more than several seconds), or to attempt to move the foot back to a normal position but have difficulty in doing so. The demeanor and training of the horse must be carefully considered—a slow response in a 3-year-old Thoroughbred in race training is abnormal, but a similar response in an aged gelding may be normal. Placing the foot (either front or rear) in a base-wide position can also be performed, and the expected response is for the horse to return the foot into a normal position. Limb placement tests in horses appear to have a low sensitivity for the detection of abnormalities of the CNS, and these tests should be coupled with careful observation of foot placement during dynamic maneuvers.

The panniculus response is tested by stimulating the skin over the trunk, then observing for a "skin-flick" response. Perianal skin reactions should be evaluated, for loss of this response is characteristic of herpes virus myeloencephalitis, for example.

GAIT ANALYSIS

The gait analysis is the process of evaluating the horse in motion at a walk and possibly trot, and when the horse is asked to perform certain maneuvers that "challenge" specific functions of the nervous system. These include waking with the head elevated, downhill, backing, turning in tight circles, or moving over or around obstacles. Specific neurological abnormalities that are observed during this phase of the examination include ataxia, paresis, and dysmetria or spasticity.

Ataxia refers to the lack of coordination of motor movements and may be categorized as vestibular, cerebellar, or sensory in origin.[6] Sensory ataxia seems to predominate in the horse, associated with spinal cord disease in which proprioceptive (ascending) input to the cerebellum is compromised. Ataxia is a description of clinical signs, rather than a specific diagnosis, and it may occur alone or with spasticity or paresis. Sensory ataxia is frequently associated with paresis,[6] and it is often difficult to discriminate between the two deficits in clinical cases. Cerebellar ataxia is seen in foals with cerebellar abiotrophy, and rarely in inflammatory disease of the CNS, and is characterized by symmetric ataxia with intention tremors and retention of

strength. Vestibular ataxia is usually associated with a head tilt and asymmetric ataxia.

Ataxia is expressed in the horse as truncal sway, weaving during walking (i.e., placing feet out of line from one step to the next), crossing over when turning, or pivoting on the inside limb when spun. Additional signs include weaving of the affected limb during the swing phase of the stride, resulting in abnormal foot placement. Many horses that are ataxic will also pace; this is significant in breeds in which the pace is not a natural gait. Signs of ataxia are most noticeable at changes of speed and direction. Careful observation of the horse when turning in hand may reveal abducted or adducted foot placement, or pivoting. If abruptly pulled up from a trot in hand, ataxic horses will often crouch and go base wide in the rear limbs. Signs of ataxia will be exacerbated when walked on a slope or with its head elevated. These deficits are similar to those seen with proprioceptive deficits, and the two disorders often co-exist.

Paresis is a deficiency of voluntary movement arising from a reduction in normal muscular power. Paresis can arise from damage to upper motor neurons (UMNs), LMNs, or muscle itself. UMN weakness results from disorders that affect the UMN or their axons in the cerebral cortex, subcortical white matter, brainstem, or spinal cord. Weakness is induced by decreased activation of LMNs and may be accompanied by spasticity. Differentiation of UMN and LMN disease may help with neuroanatomic localization and understanding the distribution of the lesion resulting in the observed clinical signs (Figure 5.2). Table 5.2 describes clinical signs that can aid in the differentiation of UMN and LMN disease.

Weak (paretic) horses have a low arc of foot flight, stumble, and have a poor response to the sway test. An additional sign of weakness in the horse is knuckling when going downhill, or difficulty when hopping on one thoracic limb ("hop test"). The sway test demonstrates an animal's ability to resist when being pushed off balance. When pushed at the withers, most adult horses should be able to resist, or quickly step sideways if pushed off

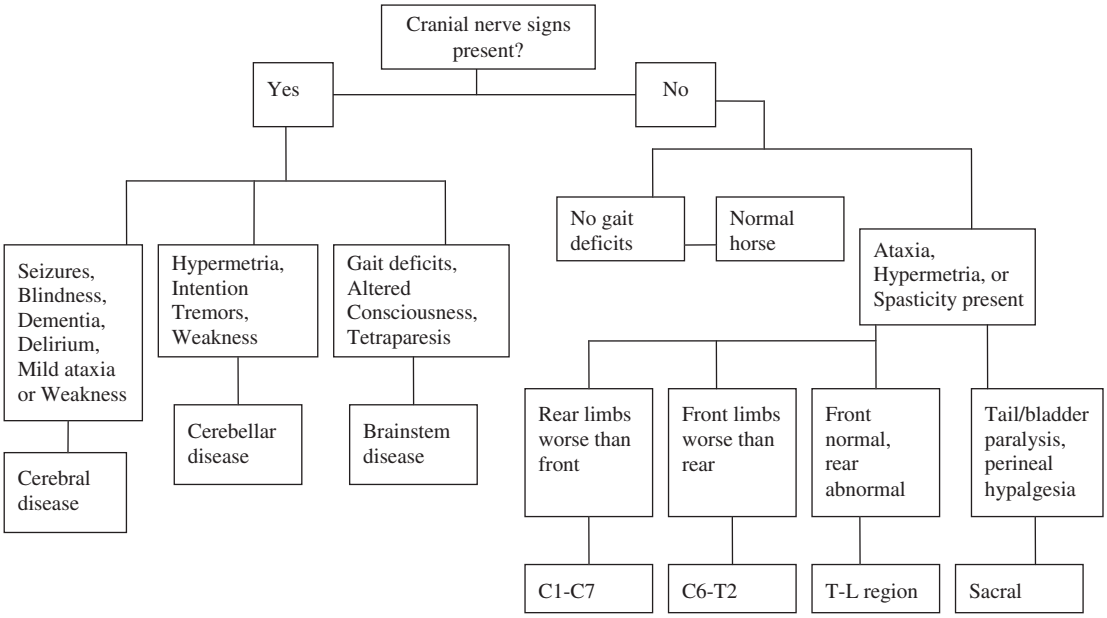


Figure 5.2. A flow chart demonstrating how the results of the neurologic examination can be used to aid the clinician in neuroanatomic localization. Ideally, the clinician should try to make one lesion explain all clinical signs. Combinations of clinical signs that cannot be explained by one site of disease imply diffuse or multifocal disease.

Table 5.2. Clinical Signs that Help to Differentiate Upper and Lower Motor Neuron Disease

Lower Motor Neuron (LMN) Weakness	Upper Motor Neuron (UMN) Weakness
Flaccid	Spasticity
Decreased tone	Increased tone
Diminished reflex response	Exaggerated reflex response
Profound muscle atrophy	Minimal muscle atrophy
Fasciculations present	Fasciculations absent

balance. Weak horses cannot resist and recover poorly (slowly) after being pushed sideways. A similar procedure is used in the rear limbs and is referred to as the "tail-pull." In this test, the horse is pulled sideways using the tail. Most adult horses can easily resist even a strong pull. This test should also be done when the horse is walking. As the horse is walking, the tail should be strongly pulled to the side then quickly released; this should be repeated several times at different phases of the stride. Normal horses should quickly correct rear limb position with the next stride, while paretic horses are more easily pulled off balance, may take several strides to recover, or interfere while attempting to correct. Horses that demonstrate good rear limb strength standing still, but are weak when walking usually have UMN disease.

Dysmetria refers to a gait in which the limb movements are either hypermetric or hypometric. A hypermetric gait is characterized with an exaggerated range of motion and excessive joint movement and is associated with cerebellar and spinal cord (spinocerebellar) disease. Hypometria is described as limb stiffness and decreased joint flexion and gives the appearance of a "tin-soldier." It is often seen as an exaggerated flight phase in horses when going downhill, or with the head elevated. Spasticity is an increase in muscle tone that primarily affects anti-gravity muscles. Spasticity is velocity dependent and demonstrates a sudden release after reaching a maximum muscle tension (the "clasp-knife reflex"). Spasticity is generally associated with UMN disease and is due to the reduced inhibition of extensor motor neurons. Spasticity is most easily demonstrated in recumbent animals, but the "bouncing" gait seen in rear limbs of horses with cervical lesions may be an expression of spasticity and exaggerated extensor tone.

The characteristic of proprioception is the ability to recognize the position of the limbs, body, and head in space. Conscious proprioception is mediated by the cerebral cortex, while unconscious proprioception is integrated by the cerebellum. Tests of proprioception commonly used in small animals are difficult to evaluate or perform in the horse, and proprioception is best evaluated by dynamic observation. An exception to this generalization may be front limb hopping, which can be performed in the adult horse. In this test, one front limb is held up, and the examiner pushes the horse sideways until the horse hops sideways to keep its balance. The authors have found this test difficult to interpret, as muscle weakness can complicate the result. In addition, the examiner must choose the footing for performing this test with care to avoid injury to the horse or examiner, should the horse fall. Clinical signs that are associated with proprioceptive loss include a base-wide stance, abnormal position of the limbs after coming to a stop, and truncal sway (if severe). When spun in a tight circle, the outside limb may be abducted, the horse may pivot on the affected limb, or cross the rear limb over the other. Extending (elevating) the head often increases the degree of incoordination and deficit. There is obvious overlap in the signs associated with proprioceptive deficit, dysmetria, and paresis, and discriminating the major component of the ataxia is often difficult.

Each examiner can establish his or her own approach to performing the gait analysis. The authors generally first observe the horse being led at a walk from the front, back, and side. It is helpful to walk alongside the horse, matching speed, and concentrate on detecting the various gait deficits. Each limb should be observed independently and is scored using the standardized scoring system.

The horse is then walked with the head elevated, and standing and walking tail pulls are performed, followed by backing the horse. Backing will exacerbate proprioceptive deficits and ataxia, which are

demonstrated by abnormal (usually base-wide) limb placement and dragging of the hooves. Limb placement, panniculus tests, and anal tone are evaluated next, and the horse is spun in a tight circle. It is important not to spin the horse for prolonged periods, as this confuses the evaluation by making the horse dizzy. The spin should be limited to about three times around, after which the examiner should then stop and allow the horse several seconds to get its balance. If necessary, the test can be repeated. The final test is to lead the horse down an incline, with the head in a neutral position, then again with the head elevated. Passive and active flexion of the neck should also be evaluated. If the neurologic signs are subtle, then jogging the horse on a straight line and in a circle is helpful to rule out musculoskeletal disease.

RECUMBENT PATIENTS

Neurologic evaluation of the recumbent patient presents unique challenges to the clinician. The effects of recumbency may alter responses and lead to complications such as peripheral neuropathies that are not part of the primary diagnosis. In addition, fear and anxiety induced by recumbency, exhaustion from struggling, or dehydration may influence the results obtained. A general observation will reveal if the horse has normal mentation, suggesting a lesion caudal to C1. If the horse can attain a dog-sitting position, demonstrating good strength and coordination of the pectoral limbs, then the lesion is likely to be caudal to T2. Loss of pectoral limb strength, while retaining the ability to lift the head and cranial neck, suggests an extreme caudal cervical lesion, such as C6–T2. The Schiff–Sherrington phenomenon describes a condition of increased forelimb tone and flaccid paralysis of the hind limbs and has been seen in horses, associated with spinal cord lesions between T2 and L4.[7]

Specific spinal reflexes can be tested in recumbent horses. Spinal reflexes require only an intact sensory nerve, spinal cord segment(s), an intact peripheral motor nerve (LMN), and muscle. Perception of the stimulus requires intact ascending sensory pathways, and horses may have an intact reflex without perception of the stimulus. In the pectoral limbs, the flexor, triceps, and biceps reflexes can be evaluated.

The flexor (withdrawal) reflex is tested by clamping the skin over the distal limb and observing for withdrawal of the limb associated with flexion of the fetlock, carpus, elbow, and shoulder. The reflex is mediated by sensory fibers in the median and ulnar nerves, spinal cord segments C6–T2, and motor fibers of the axillary, median, musculocutaneous, and ulnar nerves.[8] Peripheral nerve trauma from recumbency can lead to sensory nerve damage, and depression and/or exhaustion can lead to a diminished response; hence this reflex must be evaluated carefully.

The biceps reflex is tested by balloting the muscle belly of the biceps and brachialis muscles with a plexor and felling for muscle contraction. This reflex is mediated by the musculocutaneous nerves and spinal cord segments C6 and C7. It is more readily detected in foals and may be difficult to detect in adult horses.[8]

The triceps reflex is tested by slightly flexing the limb, then balloting the distal portion of the triceps at its point of insertion. A positive reflex is the observation of triceps muscle contraction. The reflex pathway tested involves the radial nerve and spinal cord segments C7–T1.

The patellar reflex in the rear limbs can be tested in both foals and adults. In this test, the limb is moderately flexed, and the patellar tendon balloted with a heavy plexor or the examiners hand in a "karate-chop" motion. A diminished response can be seen in horses with botulism or femoral nerve disease. Exaggerated responses to any of these segmental reflexes are associated with UMN disease cranial to the site of the spinal cord segments tested by the reflex.

EXAMINATION OF FOALS

The neurologic evaluation of foals presents some unique challenges to the equine practitioner.[9] Foal behavior, age-related changes in results, and the fact that foals are not in most cases trained to lead are complicating factors. The general examination procedure is similar for the foal; however, the gait evaluation must be accomplished with the foal at liberty following the mare. The normal newborn is able to stand by 2 h after birth. Although much time is spent down resting, the foal is readily arousable and is normally curious. Udder seeking behavior is observed after arising. When restrained, the foal often struggles briefly, then sinks limply into the examiner, which has been called "flopping." Restraint may stimulate biting or chewing movements. The

normal foal holds its head in a slightly more upright and flexed position than adults, and head movements are somewhat jerky and exaggerated. Foals are somewhat hyperresponsive to tactile stimulation. Foals are visual from birth, but the menace response is not seen until about 2 weeks of age. A pupillary light response is present, and the pupil forms a slight ventromedial angle to the palpebral fissure which is not seen in adults, and which is lost by 1 month of age. The foals gait shows exaggerated, short strides that are somewhat dysmetric, but which approach a normal adult gait by several weeks of age. This is highly variable among foals, however.

Foals can be placed in lateral recumbency to evaluate limb reflexes, which are in general exaggerated when compared to the normal adult. The triceps tendon and extensor carpi radialis tendon reflex are readily elicited in the newborn foal. A prominent crossed extensor reflex can be seen, as well as the extensor thrust reflex for the first day or two of life.

NEUROLOGIC ISSUES OF THE PREPURCHASE EXAMINATION

The neurologic examination should routinely be incorporated into the examination for purchase. The examination is performed in the same manner, and interpretation of any observed deficits is the same; however an important feature is to be aware of the association between nervous system and musculoskeletal disease. This includes such problems as osteochondrosis of the stifle, hock, and shoulder joints, which often occur concurrently in horses with cervical stenotic myelopathy (CVM). Two common historical findings of particular interest are previous medial patellar desmotomy and/or bilateral bog spavin in early life. Bog spavin is highly associated with osteochondrosis of the distal tibia, while a prior patellar desmotomy may be performed due to quadriceps weakness secondary to neurologic disease.[10] The horse should be carefully examined for any breed-related neurologic illnesses, such as cerebellar abiotrophy in Arabians. Nutritional history and housing may be important in evaluating a horse's risk of developing equine LMN disease, which is associated with dry-lot housing and lack of fresh forage. Applying a blindfold to test for compensated head tilt is useful, particularly if there is any history of head injury or trauma. As in most other body systems, the horse may demonstrate some mild or inconclusive deficits during the neurologic examination. In many cases, these may be due to subtle musculoskeletal disease, rather than neurologic disease.

DIFFERENTIATING NEUROGENIC AND MUSCULOSKELETAL GAIT ABNORMALITIES

The differentiation of neurologic and musculoskeletal disease is often problematic. Normal response during the nervous system examination requires a sound musculoskeletal system; hence musculoskeletal disease will lead to abnormalities of the neurologic examination. In particular, multiple limb lameness, or bilateral hind limb lameness, will cause horses to stumble, interfere, or pivot when spinning. These cases are particularly challenging because the characteristic gait abnormalities associated with a particular lameness will be altered by the presence of lameness in other limbs. Careful observation of the horse's gait and application of a few basic principles can simplify the process, however.

In general, the horse with a musculoskeletal problem has a gait which is regularly irregular. That is, the horse may take an abnormal step, or have abnormal placement; however, the abnormality is the same from step to step. In contrast, the gait in a horse with neurologic disease is irregularly irregular. The foot placement or step will vary from one step to the next. Furthermore, in horses with neurologic disease, the abnormality should be apparent in all phases of the gait examination, although particular maneuvers may make the signs more obvious. If a deficit is seen only during circling, for example, yet not detected during downhill, backing, or walking in a line, then hock soreness should be investigated.

Treatment of the horse with non-steroidal anti-inflammatory drugs (NSAIDs) will minimize clinical signs of musculoskeletal disease, yet will not commonly influence neurologic disorders. Hence, examination before and after treatment with NSAIDs can be a useful aid in some cases. Finally, the use of nerve blocks and joint anesthesia, followed by a repeat nervous system examination, can be done. If local anesthesia resolves the previously identified gait abnormality, then musculoskeletal disease must be the cause.

EXAMINATION OF THE PERIPHERAL NERVES

Examination of the peripheral nerves is important in the neurologic examination. Of particular interest to

Table 5.3. Grading System for Gait Analysis

Grade	Description
0	No neurologic deficits detected
1	Neurologic deficits just detected at a normal gait but worsened by backing, turning, loin pressure, or neck extension
2	Neurologic deficits easily detected at the walk and exaggerated by backing, turning, loin pressure, or neck extension
3	Neurologic deficits prominent at the walk, with a tendency to buckle or fall with backing, turning, loin pressure, or neck extension. Postural deficits noted at rest
4	Stumbling, tripping, and falling spontaneously at a normal gait
5	Horse recumbent

Modified from Mayhew, I., deLahunta, A., Whitlock, R., et al. 1978. Spinal cord disease in the horse. *Cornell Vet* 68 (Suppl 6):24–29.

Table 5.4. Clinical Abnormalities Associated with Different Segments of the Spinal Cord

Spinal Segment	Clinical Signs
C1–C5	Spastic gait, worse in rear limbs
	Proprioceptive deficits
	Weakness
	+/– Horner's syndrome
C6–T2	Proprioceptive deficits, worse in front than rear
	Weakness
	Muscle atrophy, thoracic limbs
	+/– Horner's syndrome
T3–L3	Proprioceptive deficits, rear
	Normal gait, front
	Rear limb weakness
	Spasticity, pelvic limbs
S3–S5	Urinary incontinence
	Fecal retention
	Hypalgesia tail and perianal
	Normal thoracic and pelvic
Coccygeal	Decreased tail tone
	Hypalgesia caudal to lesion
	Normal front and rear limbs

veterinarians are those peripheral nerves that innervate the limbs. Typically, disease of the peripheral nervous system is usually unilateral and limited to a single limb or region. Evaluation is performed through direct observation of function, or by reflex testing and is dependent upon knowledge of normal peripheral nerve anatomy and regions of innervation. Acute injury will result in functional loss (such as abduction of the shoulder joint, or knuckling of a distal extremity), while chronic injury will result in atrophy of the affected muscle groups.

Sensation is tested by touching a region with a sharp instrument, and pain perception is tested by grasping the skin with forceps.

Table 5.5. Clinical Signs Associated with Disease of Various Anatomic Regions of the Nervous System

Anatomic Region	Predominant Clinical Signs
Cerebral cortex	Postural deficits, seizures, altered mentation, blindness
Brain stem	Ataxia, weakness and dysmetria, mild to moderate. Dysphagia, anisocoria, or dilated pupils possible
Vestibular system	Ataxia, head tilt, postural deficits pronounced
Cerebellum	Ataxia and intention tremors
Spinal cord UMN	Paresis, ataxia, and dysmetria all present and mild to moderate. Spasticity is prominent
Peripheral nerve/LMN	Weakness predominates Postural deficits and ataxia (mild)

NEUROANATOMIC LOCALIZATION AND CASE SYNTHESIS

Once the physical examination, history, and neurologic examination are complete, neuroanatomic localization of the nervous system abnormality is determined. Differential considerations can be then be constructed and evaluated. The results of the neurologic examination should allow the examiner to determine which area or areas of the nervous system are affected. Basic neuroanatomic divisions are the cerebral cortex, brain stem, vestibular system, cerebellum, spinal cord, or peripheral nerve. In general, cranial nerve signs indicate a lesion cranial to the foramen magnum. A horse with a normal sensorium and no cranial nerve deficits has a lesion(s) caudal to the foramen magnum. Gait deficits are assigned a "score" based on the criteria described in Table 5.3. Clinical signs associated with abnormalities of different segments of the spinal cord are presented in Table 5.4. In general, cervical lesions (C1–C6) result in proprioceptive deficits, weakness, and ataxia that involve all four limbs, but are one grade worse in the rear limbs than the front limbs. A gait deficit that is worse in the front limbs than the rear suggests a lesion within the region of the brachial intumescence (C7–T2). Neurologic gait deficits that involve the rear limbs with normal front limbs indicate a lesion in the thoracolumbar region. In general, the examiner should attempt to explain the neurologic deficits observed by a single lesion site; if this is not possible, multifocal disease must exist, which is important in differential diagnosis. Clinical signs associated with various parts of the nervous system are summarized in Table 5.5. In addition, the presence of symmetry or asymmetry must be evaluated. Some conditions, such as cervical compression, cauda equina syndrome, and EDEM, are symmetrical, while others, especially EPM, are characteristically asymmetric. The history of the neurologic disease should be considered, as some conditions have an acute onset (such as fracture), while others have a more chronic or insidious course (i.e., EPM). The presence of systemic disease, fever, and anorexia is an important clue indicating the presence of an infectious disease, such as EEE, WEE, rabies, WNV, or meningitis.

REFERENCES

1. Mayhew IJ. 1989. Neurologic evaluation. In *Large Animal Neurology*, edited by Mayhew IG,15-47. Philadelphia, PA:Lea and Febinger.
2. Greet TR, Jeffcott LB, Whitwell KE, *et al*. 1980. The slap test for laryngeal adductory function in horses with suspected cervical spinal cord damage. *Equine Vet J* 12:127–31.
3. Newton-Clarke MJ, Divers TJ, Delahunta A, *et al*. 1994. Evaluation of the thoraco-laryngeal reflex ("slap test") as an aid to the diagnosis of cervical spinal cord and brainstem disease in horses. *Equine Vet J* 26:358–61.
4. Reed SM. 1998. Neurologic examination. In *Equine Internal Medicine*, edited by Reed SM, Bailey WM, 427–34. Philadelphia, PA:W.B. Saunders Co.
5. Rooney JR. 1973. Two cervical reflexes in the horse. *J Am Vet Med Assoc* 162:117–9.
6. Oliver JE, Lorenz MD, Kornegay JM. 1997. Ataxia of the head and the limbs. In *Handbook of Veterinary Neurology*, edited by Oliver JE, Lorenz MD, Kornegay JM, 216–39. Philadelphia, PA:W.B. Saunders Co.

7. Chiapetta JR, Baker JC, Feeney DA. 1985. Vertebral fracture, extensor hypertonia of thoracic limbs, and paralysis of pelvic limbs (Schiff–Sherrington syndrome) in an Arabian foal. *J Am Vet Med Assoc* 186:387–8.
8. Hahn CN, Mayhew IG, MacKay R. 1999. Nervous system. In *Equine Medicine and Surgery*, edited by Colahan PT, Mayhew IG, Merritt AM, Moore JN,863–996. St. Louis, MO:Mosby.
9. Adams R, Mayhew IG. 1984. Neurological examination of newborn foals. *Equine Vet J* 16:306–12.
10. Reed SM. 1992. The neurologic examination of the horse for purchase. In *Vet Clin North Am (Equine Practice)*, edited by Beeman GM, 377–87. Philadelphia, PA:W.B. Saunders, Co.

6
Differential Diagnosis and Management of Horses with Seizures or Alterations in Consciousness

Veronique Lacombe and Martin Furr

The clinical problem of seizures in the horse is challenging for the veterinarian to diagnose and manage, and is usually very distressing, if not downright dangerous to the owner or caretaker of adult horses. Like other problems of the central nervous system (CNS), the clinical expression of the disorder is often nonspecific, and the underlying cause may not be easily determined. This is particularly so in cases of recurrent seizures of adults, in which the horse may be clinically normal in the interictal period. Diagnosis and management is complicated by the fact that many horses (if not most) are unobserved for long periods of the day; hence inciting events may not be observed. The presence of seizures or other alterations in consciousness may be signaled by the observation of frequent superficial wounds or abrasions. Unexplained blindness or abrasions around the eyes and head are particularly evident in foals, as is impaction of soil or grass in the conjunctiva and lacerations or abrasions of the lips and mouth. This should alert the caretaker to the possibility of a seizure disorder and lead to increased observation. Caretakers must also be counseled about the potential for human injury from an adult horse suffering from a seizure. The strong inclination, among some horse owners at least, to rush in and attempt to "control" the horse can lead to serious injury and must be avoided.

A seizure (from the Latin *sacire*, "to take possession of") is a paroxysmal event which arises due to excessive discharges of the cerebrocortical neurons.[1] The abnormal electrical activity may arise in other portions of the brain or brainstem, then may spread to the cerebrum. The specific clinical presentation of the seizure depends upon the specific anatomic location and size of the electrical discharge and is independent of the etiology. Seizures, also known as fits or convulsions, are specific clinical events and are distinct from epilepsy, which is defined as reoccurring seizures from a chronic underlying process. True epilepsy appears to be very rare in the horse, and it has been suggested that it may not occur at all.

Clinical signs of seizures in horses can be variable, ranging from mild alterations in consciousness and focal muscle fasciculations to recumbency with tonic–clonic struggling. In this case, the movements are characterized by stiff, hypertonic limbs with repetitive, rhythmic struggling. The rhythmic patterned movements help to discriminate between a true seizure and merely aimless struggling from pain, anxiety, or severe orthopedic or muscle disease. In milder forms, horses do not always become recumbent, and the presence of a seizure can be confirmed only by electroencephalography. There may be a prodromal phase ("aura") during which the horse is restless or distracted, or demonstrates other changes in mentation. Following the seizure, there is usually a period of time during which the horse remains depressed and quiet, and may be blind. The blindness is usually transient in adults, but may persist for several days in foals.[2]

In the differential diagnosis of seizures in the horse, it is important to differentiate between true seizures and other disorders that may mimic seizures. Acute collapse without premonitory signs is most characteristic of a cardiovascular event, while muscle

disease, circulatory shock, and botulism may lead to muscle tremors and flailing behavior that could be confused with a seizure. In addition, narcolepsy has been described in horses and may be confused with seizures. In animals with a true seizure, the muscle movements are repetitive and rhythmical, while movements that are misdirected and variable may be associated with a horse or foal struggling to right themselves. In addition, horses with seizures are non-arousable, while horses which are frightened and struggling are somewhat responsive to the examiner. Some factors that may aid in the differentiation of these two events in the horse are presented in Table 6.1. Non-neurologic disorders which can be confused with seizures are listed in Table 6.2.

Seizures in horses can be classified as being partial, generalized, or status epilepticus.[3] Partial seizures arise from a discrete area of the cerebral cortex, with resultant localized clinical signs that may include facial or limb twitching or self-mutilation. In addition, this category of seizure can progress and spread diffusely throughout the cortex—a phenomenon termed partial seizure with secondary generalization. The progression of a very localized abnormal movement which then progresses to involve more of the extremity is termed Jacksonian march and represents a spread of the seizure focus over progressively larger areas of the cerebral cortex.[1] If consciousness is impaired, the seizure is termed a complex partial seizure. This type of seizure (complex partial) is commonly observed in neonatal foals and is commonly seen as "chewing-gum fits," jaw chomping, and lip smacking.[4] These are also referred to as automatisms, which are involuntary automatic behaviors.

Generalized seizures arise from both cerebral hemispheres simultaneously, although it is difficult in horses to determine whether there was not an initial focal seizure which progressed very rapidly to a generalized condition. This is probably the most common type observed in adult horses, but this observation has not been substantiated. Status epilepticus is characterized by a rapid succession of seizures and is considered uncommon in adult horses.[2]

Seizures may arise from a wide range of causes, which are summarized in Table 6.3. Neonates appear to have a lower seizure threshold than adults, making them more susceptible to seizures. In neonatal foals, likely causes include hypoxic ischemic encephalopathy (HIE), trauma, congenital disorders, and metabolic derangements. Persistent hyperammonemia should be considered in young Morgan horses, and severe pneumonia (with associated hypoxia) has been observed to result in seizures of weanling age horses. The most common causes of seizures in adult horses are reported to be trauma, hepatoencephalopathy, and toxicity,[2] although a large number of conditions have been reported to cause alterations in consciousness or seizures in adults as well.

Due to the numerous causes of seizures, a complete evaluation directed at eliciting both intracranial and extracranial causes should be pursued. In foals and young horses, it is important to note the breed, as young Egyptian Arabs are reported to have benign seizure events, while Morgan horses may have hyperammonemia. Travel and vaccination history should be obtained, as well as feed history and any recently administered pharmaceuticals. A physical examination should elucidate the presence of systemic, extracranial disease which may predispose to seizures. Cuts or scrapes on the head, or evidence of bleeding from the nares or ears suggest trauma, while a concurrent or recent fever may signal an infectious disorder. A complete blood cell count and serum biochemistry analysis, which includes calcium and magnesium, is indicated. If evidence of systemic disorders or hepatic disease is found, further work-up is indicated and may include liver function tests, liver biopsy, and determination of serum ammonia concentration. An arterial blood gas evaluation is indicated, particularly in foals, to

Table 6.1. Clinical Signs Which can be Used to Differentiate Between Seizures and Syncope

Feature	Seizure	Syncope
Premonitory signs	Aura	Fatigue
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30 s or longer	None or a few seconds
Disorientation after event	Several minutes or longer	Recovery almost immediate

Table 6.2. Non-Cerebral Clinical Conditions Which can be Confused with Seizure Activity in Adult Horses and Foals

Disease	Comments
Cardiovascular disease	
Atrial fibrillation	Confirm by auscultation (irregularly irregular rhythm) and electrocardiogram
Ruptured chordae tendeneae	Accompanied by the presence of pulmonary edema, abnormal auscultation
Myocardial infarction	Rarely observed; ECG abnormalities, irregular pulse
Aortic root rupture	Accompanied by pallor and very weak pulse quality
Pericarditis	Weak pulse, abnormal auscultation
Circulatory shock	
Hemorrhage	Cold extremities, weak pulse, elevated heart rate
Volume depletion	Pale mucus membranes, elevated heart rate
Electrolyte disorders	
Hypocalcemia	Muscle fasciculation, risus sardonicus
Hypomagnesemia	Muscle fasciculation, risus sardonicus, mania
Muscle disease	
Hyperkalemic periodic paralysis	Associated with hyperkalemia
Recumbency myopathy	History of recumbency, firm painful muscles
Other	
Botulism	Systemic flaccid paralysis and weakness of limbs and muscles of the head
Tetanus	Diffuse, symmetrical hypertonicity, limbs and muscles of head
Exertional rhabdomyolysis	Firm, painful muscles, pigmenturia
Post-anesthetic myelopathy	History of anesthesia with signs of spinal cord disease
Anaphylaxis	Cold extremities, weak pulse, elevated heart rate

rule out hypoxia or metabolic derangements. In the absence of systemic disease, intracranial disease must be assumed. Radiographs of the skull in both lateral and dorsoventral projection are indicated, followed by a cerebrospinal fluid (CSF) collection and evaluation. CSF collection from the atlanto-occipital space is ideal, but may be contraindicated if the horse is showing signs of increased CSF pressure, such as mydriasis or papilledema. CSF with blood is consistent with trauma, verminous migration, or tumors, while normal fluid can be seen in many conditions. CSF of normal neonates is slightly xanthochromic (up to 10 days of age),[5] but in older foals or adults, it is consistent with prior hemorrhage and/or diffuse inflammatory conditions. Elevated total protein and cell counts are commonly seen in infectious conditions but are sometimes highly variable. Culture of the CSF is indicated if there is any suggestion of sepsis. Serologic testing of serum and CSF for the viral encephalitidies is often warranted, as is testing for equine protozoal myeloencephalitis (EPM). Electroencephalography is a useful ancillary test in many situations and has been found to have a good diagnostic potential.[6] Specialized imaging modalities (such as MRI or CT scan) may be useful, but availability is limited, and these procedures are expensive. Due to their smaller size, these imaging modalities are more available for foals than adults.

MANAGEMENT OF HORSES WITH SEIZURE DISORDERS

The goals of treatment are to stop the seizure (if presently occurring), to correct the underlying disease (if determined), and to maintain a seizure-free status.

Table 6.3. Causes of Seizure or Altered States of Consciousness in Foals and Adult Horses

Developmental/malformations
Hydrocephalus
Meningoencephalocele
Dandy–Walker malformation
Numerous potential malformations
Metabolic derangement
Hepatoencephalopathy
Hypocalcemia
Hyponatremia
Hypoglycemia
Hypo/hyperosmolality disorders
Neoplastic
Cholesterol granuloma
Adenocarcinoma
Iatrogenic
Air embolism
Intracarotid injection
Post-myelography
Moxidectin overdose
Fluphenazine
Enrofloxacine overdose
Idiopathic
Hypoxic/ischemic encephalopathy
Benign epilepsy of Arabian foals
Post-anesthetic cerebral necrosis
Infectious
Bacterial meningitis/abscessation
Viral encephalitis
Verminous encephalitis
Equine protozoal myeloencephalitis
Toxic
Metaldehyde
Nardoo fern
Swainsonia
Locoweed
Datura (jimsonweed)
Buckeye (Aesculus)
Solanum
Moldy corn
Trauma
Hyperthermia

Anticonvulsant Therapy

The immediate control of seizure-like activity is a priority as prolonged or recurring seizures may result in increased intracranial pressure and neuronal necrosis.[7] Prompt control of seizures is also important to minimize the possibility of further injury to the horse or any human caretakers. Seizures in neonates may also result in reduced arterial oxygenation, which may be important in some situations. The second goal is to eliminate or at least decrease the frequency of seizures by the use of long-acting anticonvulsant therapy, without unacceptable adverse effect associated with such therapy (Table 6.4).

Diazepam, a benzodiazepine anticonvulsant, has been routinely used for short-term (immediate) control of seizures. All benzodiazepines hyperpolarize neuronal cells by binding to the gamma-aminobutyric (GABA) receptor, thereby amplifying the action of GABA on chloride channels in the cell membrane. This increased chloride conductance hyperpolarizes the neuronal cell membrane, making the cell more resistant to depolarization. The overall result is an increase in the seizure threshold and a decrease in the electrical activity of the seizure focus.[8] Diazepam is distributed rapidly to the CNS after intravenous (IV) administration and has a short duration of action (10–15 min). Because of its short half-life, repeated doses must be used, if necessary. However, caution should be exercised as prolonged usage may cause respiratory depression or arrest in foals.[9] Furthermore, care should be taken when administering repeated doses to foals less than 21 days old because of the slower clearance of the drug reported in this age group compared to older foals and adults.[9] High doses (>0.2 mg/kg) in adult horses may cause muscle weakness and ataxia, and recumbency may result.[10] Furthermore, diazepam should be used with caution in horses or foals with hepatoencephalopathy, as it may exacerbate clinical signs due to the upregulation of benzodiazepine receptors.[11] In patients that do not response to the initial course of bolus doses of diazepam, a constant rate infusion of diazepam can be implemented at an initial rate of 0.1 mg/kg/h.[7]

Midazolam is a potent short-acting benzodiazepine that has been utilized for anticonvulsant therapy in foals.[12,13] Midazolam has been recommended at the dose of 0.05–0.1 mg/kg IV or intramuscular (IM); the smallest effective dose should be used and can be repeated as needed. Midazolam can also be

Table 6.4. Main Mechanisms of Action of Anticonvulsant Drugs Used for Horses and Foals

	Mechanisms of Action			
	Decrease Seizure Onset		Decrease Seizure Spread	
Anticonvulsant Drugs	Enhanced Na^+ Channel Inactivation	Enhanced GABA-Activated Cl^- Conductance	Reduced Current Through Ca^{2+} Channels	Reduced Glutamate-Mediated Excitation
Main				
Benzodiazepines		++		
Phenobarbital		++	+	+
Bromide		++		
Alternative				
Phenytoin	++			
Primidone		++	+	+

++ Postulated primary mechanism of action. Modified from Podell (2001).[40]

administered by continuous rate infusion in foals with recurrent seizures (1–3 mg/h for a 50-kg foal).[12] Midazolam has been proven to be highly effective for controlling status epilepticus and seizures that are refractory to phenobarbital and/or phenytoin in human infants. No pharmacological studies have been reported in horses.

Other sedative drugs should be used with caution for emergency seizure management. For instance, xylazine reduces cerebral blood flow after transiently increasing intracranial pressure, which may potentially exacerbate cerebral edema and worsen seizures.[14] Acepromazine is contraindicated since it may reduce the seizure threshold.[2] Historically, ketamine has also been contraindicated since it increases intracranial pressure and may exacerbate seizure-like activity.[14] However, ketamine also acts as an antagonist of *n*-methyl-D-aspartate (NMDA) receptors, which have been implicated in the pathogenesis of seizures in infants.[15,16] In support of this, ketamine infusion has been proven to control seizure activity in a rodent model of status epilepticus refractory to phenobarbital,[17] although the proof of a similar beneficial effect in a clinical setting is currently lacking.[18] Thus, the use of ketamine in the treatment of horses with seizures remains unclear (Table 6.5).

Once the initial seizure has been controlled, it must be determined whether prophylactic anticonvulsant therapy is warranted. This is a major commitment for the veterinarian and owners as the anticonvulsant may be administered for a minimum of several months before discontinuing. Furthermore, the owners must realize that seizure control does not necessary imply complete elimination of the episodes, but rather a decrease in the frequency and severity of the seizure-like activities. The decision to initiate anticonvulsant drug therapy depends on the underlying cause, seizure type, and frequency. Although rarely reported in horses, status epilepticus warrants the use of anticonvulsant therapy. Status epilepticus is defined as more than 30 min of continuous seizure activity or two or more sequential seizures without a full recovery of consciousness.[19] With identified intracranial diseases, the therapy should be initiated at the onset of seizures. When no specific etiology has been determined and a presumption of idiopathic epilepsy has been made, criteria for beginning maintenance anticonvulsant therapy include increased frequency, duration and/or severity (e.g., cluster of seizures, at least one seizure occurring at least every 2 months), or the presence of generalized repeated seizures resulting in recumbency or self-injury.[20,21] A useful aid for determining the need for maintenance anticonvulsant therapy is to have the owners keep a log to document any observed seizures, with a recording of the date and time of day, duration, behavior of the horse in the interictal period, and any associated event which may be triggers. Video documentation

Table 6.5. Guidelines for Treating Convulsing Adult Horses

Objectives	Type of Treatment	Dosage	Route	Frequency
Control convulsions: initial therapy	Diazepam	0.05–0.2 mg/kg in 25–100 mg doses	IV or IM	As needed
	Phenobarbital	12–20 mg/kg initial dose (diluted in saline over 30 min), then 1–9 mg/kg	IV	q 8–12 h after initial dose
	Phenytoin	1–5 mg/kg		q 4h for up to 24h
	Pentobarbital	2–10 mg/kg	IV or PO	To effect
	Chloral hydrate	33.3–133.3 mg/kg	IV	To effect
	Guaifenesin	88.9–133.3 mg/kg	IV	To effect
Prevent convulsions: maintenance therapy	Phenobarbital	5–11 mg/kg	PO	q 12–24 h
	Potassium bromide	25–40 mg/kg	PO	q 24h
	Phenytoin	1–5 mg/kg	PO	q 12 h
Control cerebrocortical edema	Dexamethasone	0.1–0.25 mg/kg	IV	q 6–24 h
	Methylprednisolone	(a) 30 mg/kg followed by 15 mg/kg 2 and 6 h later, followed by a CRI (2.5 mg/kg/h)	IV	First dose within 4 h after trauma
		(b) 100–1000 mg	IV	CRI for 48 h
	DMSO	1.0 g/kg diluted as a 10% solution	IV	q 12–24 h
	Mannitol	0.25–2g/kg as a 20% solution	IV	q 12–24 h
	Furosemide	1 mg/kg	IV, IM, SQ	q 12h
Antioxidant and NMDA receptor blockade therapy (efficacy not established, only based on human studies)	Alpha-tocopherol (vitamin E)	(a) 2000 IU/adult	IM	Once, with PO
		(b) 5000–20,000 IU/adult	PO	q 24 h

	Ascorbic acid (vitamin C)	20 mg/kg	PO	q 24 h
	Allopurinol	5 mg/kg	PO	q 12 h
	Magnesium sulfate	50 mg/kg	IV slow	Once
Provide proper hydration and nutritional support	Cautious fluid therapy Oral feeding (if tolerated)		IV	
Correct metabolic derangements (if needed)	Oxygen therapy Glucose supplementation		Nasal IV	
Minimize chances of trauma	Provide thick bedding, heavy padding, helmet, and leg wraps			

Modified from Sihna and Cox (1995),[37] MacKay (2004),[45] and Hines (2003).[46]

of seizures is optimal if it can be performed under safe conditions. In neonatal foals, if more than three doses of diazepam are needed over a few hours to control seizures, anticonvulsant therapy should be initiated because of their greater duration of activity (Table 6.6).[11]

Options for anticonvulsant maintenance therapy include phenobarbital, bromide, phenytoin, and primidone. Phenobarbital is the drug of choice in horses. Although phenobarbital has been used to treat epilepsy for over 80 years, the mechanisms of action are not fully elucidated. Phenobarbital facilitates neuronal stabilization via GABA receptors in postsynaptic neurons of inhibitory nerve terminal, increasing intracellular chloride conductance. Other mechanisms include inhibition of postsynaptic potentials produced by glutamate and inhibition of voltage-gated calcium channels at excitatory nerve terminals.[22] Phenobarbital is well absorbed after oral administration, with a bioavailability close to 100% in horses.[23] The majority of the drug is metabolized in the liver, with approximately 25% excreted as unchanged drug in horses.[8] Phenobarbital induces the hepatic cytochrome P450 enzyme complex, resulting in a more rapid metabolism not only of phenobarbital but also of other concurrently administered drugs. For instance, the elimination half-life after a single oral dose of phenobarbital is reduced from 24 h (initial) to 11 h after 42 days of treatment in horses.[24] Therefore, dosage adjustment may be required after long-term therapy to maintain serum concentrations within the therapeutic window.

The half-life of phenobarbital in horses is shorter than in humans and small animals (~18 h with a range of 14–24 h for initial elimination half-life in adult and ~12 h in foals after IV administration), in part because a smaller proportion of the drug is protein bound.[23–26]

The goal of any antiepileptic therapy is to achieve a therapeutic steady-state condition, which is usually reached within five to six elimination half-lives. Given the variability in half-life, clearance, and metabolism of phenobarbital, as noted above, therapeutic monitoring is necessary to ensure that adequate anticonvulsant concentrations are obtained, and toxicity avoided. Thus, the peak concentration (which occurs 2 ± 1.5 h after oral dose administration in adults), and the lowest (trough) concentration (which occurs just before the next dose) should be determined after 4–5 days of treatment in adult horses and 3 days in foals.[24] The suggested therapeutic serum concentration, extrapolated from studies in humans and dogs, is 15 to 45 μg/ml (70–175 μmol/l) in adult horses.[8] Monitoring of trough phenobarbital level should be done when seizure control is inadequate, when toxic side effects are seen, or after a dosage adjustment. Furthermore, as mentioned above, dosage adjustment may be required after long-term therapy; and we recommend, as a rule of thumb, serial monitoring of the trough phenobarbital concentration at 14, 45, and every 60 days after initiation of treatment, if the horse appears to be seizure free. Although phenobarbital monitoring is important especially in cases with inadequate seizure control, the clinical response to therapy is as important in overall management. Thus, based on the initial clinical response (which varies between horses) and based on therapeutic serum concentrations (if needed), the dose of phenobarbital may be adjusted using the following formula:

$$\frac{[\text{Desired peak serum}]}{[\text{Measured peak serum}]} \times \text{Old dose} = \text{New dose}^{8}$$

The effects of hepatic induction and changes in body weight due to growth suggest that therapeutic monitoring is particularly important in foals. Furthermore, foals have altered distribution patterns and elimination characteristics of drugs due to greater extracellular fluid volume and lower concentrations of plasma-binding proteins compared to adults. Therefore, neonates may have significant clinical effects at lower serum concentrations.[27] Indeed, an effective nontoxic therapeutic range of 5–30 μg/ml in foals has been reported (Table 6.7).[13]

In an emergency situation, intravenous phenobarbital should be used because it rapidly (within 20 min) provides a high serum concentration to stop seizures, as well as reducing cerebral metabolic rate.[22] Increase in cerebral oxygen consumption has been associated with seizure activities and will induce an increase in cerebral blood flow to match the enhanced oxygen demand, which may result in an increased intracranial pressure.[28] Thus, reduction of metabolic rate is important particularly if cerebral edema is suspected. As a result of pharmacological studies in foals, it has been recommended to use a loading dose of 20 mg/kg (diluted in 30 ml of saline and infused intravenously over a 30-min

Table 6.6. Therapeutic Guidelines for Treating Convulsing Foals

Objectives	Type of Treatment	Dosage	Route	Frequency
Control convulsions: initial therapy	Diazepam	0.1–0.4 mg/kg slow	IV	As needed
	Midazolam	0.05–0.1 mg/kg	IV or IM	As needed
	Phenobarbital	9–20 mg/kg loading dose (30 ml saline)	IV	
	Phenytoin	5–10 mg/kg	IV	
	Primidone	20–40 mg/kg	PO	
	Pentobarbital	2–4 mg/kg	IV	To effect
	Chloral hydrate	66.6–222.2 mg/kg	IV	To effect
	Guaifenesin	To effect	IV	To effect
Prevent convulsions: maintenance therapy	Phenobarbital	(a) 4–10 mg/kg	PO	q 12 h
	Phenytoin	(b) 2–10 mg/kg	IV	q 8–12 h
	Primidone	1–5 mg/kg	PO, IM	q 2–4 h for 12 h, then q 6 h or q 12 h
		—	—	
		15 mg/kg	PO	q 12 h
Control cerebrocortical edema	Prednisolone	50–10 mg/kg	IV	
	DMSO	0.5–1.0 g/kg diluted in 10% solution	IV	q 12 h
Antioxidant and NMDA receptor blockade therapy (efficacy not established in HIE foals, only based on human studies)	Alpha-tocopherol (vitamin E)	500–4000 units per foal	PO	q 24 h
	Ascorbic acid (vitamin C)	50–100 mg/kg	IV	q 24 h
	Allopurinol	40 mg/kg	PO	Within first 4 h
	Magnesium sulfate (HIE)	50 mg/kg/h for the first hour diluted to 1% as a loading dose, then 25 mg/kg/h CRI	IV	CRI q 24–48h
Provide respiratory support (if needed)	Oxygen supplementation	5–10 l/min	Nasal	

(*continued*)

Table 6.6. (*continued*)

Objectives	Type of Treatment	Dosage	Route	Frequency
	Caffeine	Loading dose 10 mg/kg	PO	
	Positive pressure ventilation	Maintenance dose 2.5–3.0 mg/kg	PO	q 24 h
Provide proper hydration and nutritional support	Cautious fluid therapy	Maintenance 4–5 ml/kg/h	IV	
	Oral feeding (if tolerated)	Milk: 10–25% of foal's body weight/day		
	Parenteral nutrition			
	Support body temperature			
Provide metabolic support	Glucose supplementation	—	IV	
	Electrolyte supplementation	—	IV or PO	
	Thiamine (HIE)	10 mg/kg	IV	q 12 h
Minimize chances of trauma	Provide thick bedding, heavy padding and head helmets, leg wrap	—	—	—

NMDA, *n*-methyl-D-aspartate; HIE, hypoxic ischemic encephalopathy.
Modified from Furr (1996),[4] Sihna and Cox (1995),[37] and Slovis (2003),[53] Vaala (2002).[55]

Table 6.7. Guide to maintenance anticonvulsant therapy to help control seizures in epileptic adult horses

Be certain that an epileptic seizure has occurred
The goal of this therapy is to eliminate or to reduce the frequency of seizures, without any adverse side effects
Set up realistic expectations with the owners. Warn owners that horse suffering from seizure disorders (even under anticonvulsant therapy) may not be safe to be around or to ride
Have the owners keep a diary of seizure activity and a medication record
Select a single anticonvulsant therapy (preferably start with phenobarbital)
Begin at the recommended dose and adjust the dose until seizures are controlled without inducing toxicity (increasing the dose by 20% every 2 weeks has been proposed, or adjust using formula described in text). The dosage must be titrated to the need of each individual horse
Monitor blood anticonvulsant concentrations, adjusting the dose to maintain the concentration within the therapeutic ranges (phenobarbital: 15–45 µg/ml; bromide: 1–3 mg/ml)
If no toxic side effects are seen, do not begin decreasing the dose or altering the frequency of medication until after the horse has been seizure free as described in text
For economic and practical purposes, it is desirable to stop anticonvulsant maintenance therapy. Discontinue slowly; sudden withdrawal of drugs may precipitate seizures. If seizures reappear, continued and perhaps life-long treatment must be considered. The horse should be reevaluated, perhaps including repeat electroencephalography
If the side effects are unacceptable (e.g., excessive sedation with phenobarbital or collapse with phenytoin) and seizures are not controlled with only one anticonvulsant therapy, reduce dose of the first drug by 20% or to nontoxic levels and begin a second drug at the recommended dose (e.g., potassium bromide).
If the seizures are controlled with the administration of the two drugs for 6 months, slowly wean the patient off one drug at a time over 3 months. If seizures begin, increase the dose again
Beware of interactions when other drugs are used in patients on anticonvulsant therapy (e.g., tetracyclines, chloramphenicol, and ivermectin). Avoid use of drugs with known interactions
Treat the underlying disorders, if identified

Modified from Mayhew (1989, 2003) and Podell (1998).[7,21,30]

period), followed by maintenance doses of 9 mg/kg IVq 8 h.[26] In adult horses, a parenteral loading dose of 12 mg/kg IV, followed by 6.65 mg/kg IV (20 min infusion) q 12 h,[25] is adequate to reach appropriate therapeutic concentrations. Maintenance therapy is usually administered by the oral route, with a proposed dose of 11 mg/kg once q 24 h in adults,[23] although the half-life of phenobarbital is unknown after oral maintenance therapy in foals.

Overall, phenobarbital is well tolerated in horses. The major reported side effect is drowsiness. Sedation may also occur in neonatal foals up to 8 h after phenobarbital administration discouraging them from nursing.[26] Furthermore, phenobarbital may cause respiratory depression, bradycardia, hypotension, and hypothermia in neonatal foals, especially at larger doses.[12] Therefore, the lowest effective concentration should be administered in conjunction with monitoring of serum drug concentration. Furthermore, foals receiving phenobarbital should have their body temperature, blood pressure, and respiratory rate monitored.[29] Veterinarians should also be aware of interactions if other drugs are prescribed in patients on anticonvulsant therapy. For instance, tetracyclines and chloramphenicol inhibit hepatic microsomal enzymes, thereby prolonging the

effects of phenobarbital and phenytoin.[30] Furthermore, ivermectin, a GABA blocker, should not be given to horses and foals on anticonvulsant therapy because of the risk of breaks in seizure control that have occurred following its use.[21,30]

Bromide (sodium or potassium) is another anticonvulsant drug which can be used in the horse.[13,31] Potassium bromide is the oldest anticonvulsant drug and was first used in 1857 to treat seizures in people. Potassium bromide has experienced a resurgence of its use in the management of canine epilepsy, and more recently in horses that were refractory to phenobarbital (e.g., inadequate control of seizures despite adequate to high serum phenobarbital levels). Although the mechanisms of action are not well known, bromide appears to compete with chloride ions to hyperpolarize (and thus stabilize) neuronal cell membranes.[7] It may also act synergistically with other drugs with GABAergic activity, such as barbiturates to increase the seizure threshold. As the elimination half-life of bromide in horses is 3 to 5 days (shorter than in cows or dogs), it takes several weeks to achieve steady-state concentrations. Hence, potassium bromide should not be the sole agent used to treat ongoing seizures.[31,32] Potassium bromide (initial dose of 25–40 mg/kg/ day PO) should be administered in combination with phenobarbital. The suggested therapeutic concentration, based on a study in dogs, is 1–3 mg/ml when used as a monotherapy and 1–2 mg/ml when used in combination with phenobarbital.[33] When used as monotherapy in horses, a loading dose of 120 mg/kg daily over 5 days followed by a maintenance dose of 40 mg/kg/day was associated with a serum concentration of 1 mg/ml, which is within the therapeutic window reported in other species.[31] Toxic effects have been reported in dogs with serum concentration above 2.7 mg/ml.[34,31] Bromide toxicosis (bromism), which can occur in people with chronic oral administration, appears to be rare in horses. One study reported bromide toxicity in horses fed hay that contained bromide ion residue from accidental treatment with methyl bromide. Signs included lethargy, hind limb weakness, and ataxia or recumbency.[35] Overall, bromide administration appears to have few complications and is considered a safe therapeutic agent, although the clinical efficacy has not been evaluated for long-term management of horses with seizures.[13] Bromide will artificially increase the assayed concentration of serum chloride, if performed using an ion-specific electrode, and should be suspected as the cause of apparent hyperchloridaemia.[32]

Although phenytoin is not routinely used as an anticonvulsant in horses, it may be considered as an alternative therapy if previous drugs are ineffective. Phenytoin appears to inactivate voltage-dependent neuronal sodium channels, to prevent depolarization of the presynaptic neuronal membrane at the excitatory nerve terminal, and thus to reduce release of glutamate, the excitatory neurotransmitter. Glutamate binds to the NMDA receptors, which opens sodium and calcium channels, leading to entry of these ions in the neuron and to postsynaptic depolarizations.[7] The bioavailability of phenytoin in horses is quite variable; hence serum phenytoin concentrations should be determined during treatment.[36] A serum steady-state concentration of 5–20 μg/ml is sufficient for effective seizure control based on human studies.[36] Side effects of phenytoin include prolonged depression in the foal, mild atrioventricular block, and decrease in blood pressure.[13,37]

Sodium pentobarbital may be used to control seizures in horses or foals, which are unresponsive to other drugs. Pentobarbital is not a true anticonvulsant; however seizure control arises due to its anesthetic effects. This anesthetic agent has profound depressant effects on respiration with repeated doses.[38] Doses of 2–10 mg/kg IV to effect are recommended and have been used. Sodium pentobarbital has little use in the management of seizures in adult horses, but may be used in the short-term management (1–3 days) of seizures in neonatal foals.

Primidone is metabolized to phenobarbital, which is the main active metabolite, and to a smaller extent to phenylethylmalonamide, other active metabolite which may potentiate the anticonvulsant effects of phenobarbital. Although primidone has been reported anecdotally for treating foals with seizures,[38,39] its use is not advised to treat epileptic horses since pharmacokinetic properties and clinical effects are unknown.

Newer antiepileptic drugs have been introduced in veterinary medicine, with improved therapeutic indices (i.e., effective dose compared to toxic dose) with a reduction of the sedative and organ-toxic adverse reactions.[40] These drugs include felbamate, gabapentin, clorozepate, toparimate, and zonisamide and can be used as monotherapy or in combination with bromide. However, the cost of these new antiepileptic drug therapies may prohibit their use in

adult horse, and their clinical efficacy and pharmokinetic properties are currently unknown.

It is difficult, if not impossible, to give a precise recommendation for when to terminate anticonvulsant therapy. The duration of the seizure-free period required before terminating anticonvulsant therapy is unknown and will depend upon the severity and frequency of the seizures prior to commencing therapy. As a general rule, the horse should be seizure free for at least 1 month if the seizures were occurring every few days. If the seizures were less frequent and well documented, then the seizure-free period should be a multiple of at least three times the duration of the seizure cycle. That is, if the horse was having a seizure roughly every 2 weeks, then the seizure-free period should be at least 6 weeks (2 weeks times 3). These are only guidelines, however, and each case must be determined individually. If therapy has reduced the severity or frequency of the seizures, but not totally eliminated them, then termination of anticonvulsant therapy is not advised. Abrupt discontinuation of the anticonvulsant therapy may precipitate seizures; hence a protocol of tapering doses is recommended. In neonates, the dose can be decreased by one-fourth to one-half each day for a minimum of 3 days, then discontinued. In the adult that has been on anticonvulsant maintenance therapy long term, a longer weaning period is suggested, decreasing the dose by 20% every other day for 1 week before stopping.[20]

In humans and small animals, serial electroencephalograms have been shown to be very useful in the management of epilepsy, in particular to monitor the need and response to treatment, to aid in establishing the probability of recurrence, and prognosis.[41–43] This practice has been limited in horses. However, based on our experiences and others,[43] horses may be seizure free on anticonvulsant therapy but still have abnormal electroencephalogram recording. Therefore, serial electroencephalograms may provide valuable information on the progression or resolution of the disease and may help the clinician in determining whether continued maintenance anticonvulsant therapy is necessary. Obviously, continued presence of an abnormal EEG suggests the need for continued anticonvulsant medication.

Although rare, horses may suffer from status epilepticus, which may not be controlled effectively with regular anticonvulsant therapy. Although an anesthetic protocol for this patient population has not been investigated, general anesthesia may be induced by a combination of guaifenesin (50 mg/kg IV to effect as a 5% solution) and thiopental (5 mg/kg IV) as an initial bolus, followed by a continuous infusion of pentobarbital (0.005 mg/kg/min) for up to 24 h.[44] Supportive care under general anesthesia should include the use of a padded stall and IV broad-spectrum antibiotic treatment. Maintenance phenobarbital therapy should be administered throughout anesthesia. An endotracheal tube may be placed if ventilation is required. In cases where cerebral edema is suspected such as after head trauma, constant ventilatory control is crucial during the entire period of anesthesia to avoid increase in cerebral blood flow and subsequent increase in intracranial pressure secondary to hypercapnia and/or hypoxia (e.g., $PaCO_2$ and PaO_2 should be maintained between 25 and 35 torr and 100 and 150 torr, respectively).[28] Ventilation-induced hypocapnia has been proposed as a means to decrease intracranial pressure, but extreme hyperventilation ($<$25 torr) will result in poor cerebral perfusion.[28,45] Furthermore, blood pressure should be maintained within the physiological range to sustain adequate cerebral perfusion. In cases of seizures refractory to all the above therapeutic interventions, gas anesthesia with isoflurane (with the least effect on elevation of intracranial pressure) may be considered. This is only a reasonable option if there is compelling reason for the clinician to expect resolution of the inciting cause of the seizure, or to provide time for conventional anticonvulsants to be administered and be fully effective. If severe generalized seizures have occurred with no response to anticonvulsant therapy, euthanasia should be recommended on humane grounds.

Finally, it should be recommended that horses not be ridden while on anticonvulsant therapy and the horse remains free of seizures for at least several months. Breeding horses suffering from seizures may be considered as an alternative.

Ancillary Therapy

The main principles of ancillary therapy in the treatment of equine seizures are (1) to control cerebral edema, CNS inflammation, and intracranial pressure, (2) decrease the production of oxygen-derived free radicals, (3) prevent post-traumatic

autodestruction of nervous tissue, and (4) provide appropriate supportive care.

Control of inflammation can be achieved by the use of steroidal or nonsteroidal anti-inflammatory drugs. Glucocorticoids stabilize microvascular permeability and decrease seizure foci.[8] Dexamethasone is the most commonly used corticosteroid for treating horses with neurological diseases, including brain and spinal cord trauma, cerebrocortical edema, viral encephalitidies, and EPM. However, it has been reported that high-dose prednisolone is more effective for recovery of small animals with neurological diseases.[46] Furthermore, short-acting glucocorticoids such as prednisolone sodium succinate are recommended in foals instead of long-acting corticosteroids.[11] In the past, glucocorticoids were contraindicated for the treatment of bacterial meningitis. However, it has been demonstrated in infants that treatment with dexamethasone reduces CSF pressure and inflammation, and lowers CSF cytokine concentration without delaying CSF sterilization by the concurrent administration of antibiotics.[47] Therefore, corticosteroid administration should be considered in convulsing foals with bacterial meningitis. Nonsteroidal anti-inflammatory drugs (e.g., flunixin meglumine, ketoprofen, vedaprofen, or phenylbutazone) have also been shown to be beneficial in the treatment of CNS inflammation in horses.[8]

Dimethyl sulfoxide (DMSO) has anti-inflammatory properties, which may be beneficial in convulsing horses, because of its abilities to stabilize membranes and scavenge free radicals that are released during inflammatory and ischemic processes.[48] DMSO is indicated for the treatment of increased intracranial pressure and/or cerebral edema, for HIE and for the acute treatment of EPM.[49,50] DMSO, at a dose of 1 g/kg, is safe as a 10% diluted solution; however, concentrations greater than 20% may cause IV hemolysis, diarrhea, and muscle tremor.

Mannitol is also used to control cerebrocortical edema; however, it is contraindicated in cases of intracranial hemorrhage as it may exacerbate bleeding.

Other medications, which may be used for their antioxidant properties, include alpha-tocopherol (vitamin E) and ascorbic acid (vitamin C). Vitamin E has been recommended at high dose (20,000 IU/adult) for horses suffering from brain trauma, although its clinical efficacy is not proven.[45] Similarly, the clinical efficiency of ascorbic acid, which has also NMDA receptor blockage properties, is unknown in horses. Finally, allopurinol, a xanthine oxidase inhibitor and thus antioxidant, has been used in hypoxic ischemic human neonates.[51] There are anecdotal reports of its use in equine neonates with HEI and in adult horses suffering from brain injury after head trauma; however its clinical efficiency is also unknown.[45,52,53]

Supportive Care

The primary principles of supportive care are to:

1. provide proper hydration and nutritional support (especially in horses and foals unable or unwilling to drink and/or eat), ensuring proper cerebral perfusion and adequate delivery of nutrients and oxygen to the brain
2. provide metabolic support to minimize factors that trigger cell death
3. treat skin trauma and limit injury associated with seizures or recumbency.

Maintaining cerebral perfusion is achieved by careful administration of intravenous fluid, especially in horses with cerebral edema and in recumbent animals for which the metabolic rate is decreased. In foals, judicious administration of inotropes may be necessary to maintain adequate perfusion pressures.

In foals presenting in status epilepticus, maintaining a patent airway is the first priority. Foals with mild hypoxia should be maintained in sternal position as much as possible, and/or by intranasal administration of humidified oxygen. Other measures as necessary to ensure adequate oxygenation and perfusion should be employed and will be directed on an individual basis.

Any electrolyte and acid–base imbalance should be corrected, especially in case of renal or hepatic disease. Moderate-to-severe hypoglycemia secondary to impaired gluconeogenesis has been reported in horses suffering from hepatic encephalopathy, and glucose supplementation resulted in remission of neurological signs in some instance.[54] Although it rarely causes seizures in neonatal foals, hypoglycemia should be promptly corrected with a constant infusion of glucose.

Recent areas of investigation and potential therapeutic targets in human medicine have been related to cellular metabolic dysfunction in relation with brain damage. For instance, NMDA receptors mediate calcium influx into postsynaptic neurons, and if

exacerbated during perinatal asphyxia, intracellular calcium overload causes neuronal necrosis by activation of lytic enzyme systems and nitric oxide synthase with generation of free radicals.[53] It has been recently suggested that magnesium sulfate, an NMDA receptor antagonist, given as an infusion, may decrease the incidence of seizures in foals suffering from HIE (Wilkins 2003).[29] Given that magnesium sulfate improves neurologic outcome after brain impact injury in an animal model, it has also been proposed for the treatment of brain injury after head trauma in adults at a dose of 50 mg/kg (25 g/500-kg horse administered in the first 5–10 l of IV fluid).[45] Thiamine administration may prevent glutamate-induced and NMDA receptor-mediated cell death in foals with HIE.[55] Furthermore, thiamine is an essential coenzyme in glucose utilization by the brain, which will further provide metabolic support.[7]

Finally, horses must be maintained and housed in a proper environment to enhance delivery of medication, ensure safety of attending personnel, and provide protection for the horse. The horse should be placed in a padded stall with heavy bedding and away from other horses. If tolerated by the horse, a protective helmet should be placed, especially on recumbent animals, which will prevent eye and head injuries. It is important to be sure that the helmet fits properly, as an ill-fitting helmet may lead to more problems than using no helmet. Maintaining horses with the potential for seizures in a sling is very dangerous and should be avoided. Security measures should be in place for all staff and owners to prevent injuries to persons treating horses with seizures. The immediate environment should be quiet, and in some cases plugging the ears with cotton is helpful. The intensity of the lighting should not be suddenly increased, to minimize the potential effects of outside stimuli.

Treating the Underlying Cause

In horses with seizures, every effort should be made to identify the etiology, and specific therapy directed toward that diagnosis should be employed. Specific treatment protocols for the numerous disorders that can lead to seizures in horses are detailed in other chapters within this text.

NARCOLEPSY

Narcolepsy is described as a syndrome of uncontrollable "sleep attacks" which are usually accompanied by complete loss of muscle tone (cataplexy). Narcolepsy has been recognized in a variety of domestic animals, including horses. Originally described in the equine literature in 1924 in a group of Suffolk foals, it has been reported in a variety of other ages and breeds.[56–59] The pathophysiology of this disorder remains undetermined, yet a familial association in Shetland ponies, American miniature horses, and Suffolk horses has been proposed.[59]

Clinical signs noted with the condition suggest two different forms of the disorder—a condition of foals and a condition which develops later in life.[60] The severity of clinical signs in newborn foals appears to be variable with some spontaneous recovery noted, with persistence in other cases, particularly Suffolk and Shetland foals. Clinical signs appear to vary between individuals and episode.[60] Most commonly, horses are noted to have a progressive lowering of the head, followed by a buckling of the forelimbs, from which horses recover or which may result in falling. In severe attacks, total recumbency with areflexia and rapid eye movement can be seen and provide the most compelling clinical evidence for a diagnosis. The ability to arouse the horse from this state varies. Once awake, the horses can regain their footing normally and appear to have normal neurologic examination. Horses remain neurologically normal between attacks. Clinical examination may find evidence of superficial trauma, particularly to the front of the fetlocks and carpi. The attacks can occur spontaneously, but have also been reported to be incited by particular events such as saddling or grooming.

In its most severe form, the syndrome is characteristic; however in less severe manifestations, diagnosis is challenging. It must be differentiated from syncope and seizures. Diagnosis is made based on the observation of excessive drowsiness at inappropriate times, evidence of cataplexy, and/or the response to provocative testing with physostigmine (0.05–0.1 mg/kg slow IV). The diagnostic accuracy of this method is questionable, at least anecdotally, however, as several horses with compelling clinical signs have failed to respond to provocative testing. Complete blood cell counts and serum biochemistry analysis, as well as CSF evaluation, are normal.

Treatment with imipramine (250–750 mg orally) has been suggested,[57,59,60] with variable success. The prognosis is guarded, and some horses with

adult-onset narcolepsy become unmanageable and dangerous, requiring euthanasia. The condition appears to be persistent in affected Suffolk and Shetland foals, but spontaneous recovery can be seen in other breeds.

REFERENCES

1. Lowenstein DH. 2005. Seizures and epilepsy. In *Harrisons Principles of Internal Medicine*, edited by Kasper DL, Fauci AS, Lngo DL, Braunwald E, Hauser SL and Jameson JL, 2357–72. New York:McGraw-Hill.
2. Mayhew IG. 1983. Seizure disorders. In *Current Therapy in Equine Medicine*, edited by Robinson NE, 344–9. Philadelphia: W.B. Saunders Co.
3. Andrews FA, Mathews H. 1998. Seizures, narcolepsy and cataplexy. In *Equine Internal Medicine*, edited by Reed SM, Bayly W, 451–57, Philadelphia: W.B. Saunders Co.
4. Furr M. 1996. Perinatal asphyxia in foals. *Compend Contin Educ Pract Vet* 18:1342–51.
5. Furr MO, Bender H. 1994. Cerebrospinal fluid variables in clinically normal foals from birth to 42 days of age. *Am J Vet Res* 55:781–4.
6. Lacombe VA, Podell M, Furr M, *et al*. 2001. Diagnostic validity of electroencephalography in equine intracranial disorders. *J Vet Intern Med* 15:385–93.
7. Podell ML. 1998. Antiepileptic drug therapy. *Clin Tech Small Anim Pract* 13:185–92.
8. Dowling PM. 2004. Drugs acting on the neurological system and behavior modification. In *Equine Clinical Pharmacology*, edited by Bertone JJ, Horspool LJ, 145–54. Philadelphia: W.B. Saunders Co.
9. Norman WM, Court MH, Greenblatt DJ. 1997. Age-related changes in the pharmacokinetic disposition of diazepam in foals. *Am J Vet Res* 58:878–80.
10. Muir WW, Sams RA, Huffman R, *et al*. 1982. Pharmacodynamic and pharmacokinetic properties of diazepam in horses. *Am J Vet Res* 43: 1756–62.
11. Furr M. 1996. Managing seizure disorders in neonatal foals. *Vet Med* 91:772–8.
12. Wilkins PA. 2005. How to use midazolam to control equine neonatal seizures. *Proc Annu Meeting Am Assoc Equine Pract* 51:279–80.
13. Magdesian KG. 2006. Intensive care medicine. In *The Equine Manual*, edited by AJ Higgins, JR Snyder, 1255–1326. Philadelphia: W.B. Saunders Co.
14. Andrews FM, Matthews HK. 2004. Seizures, narcolepsy and cataplexy. In *Equine Internal Medicine*, edited by Reed SM, Bayly WM, and Sellon DC, 560–66. St. Louis: Saunders.
15. Trommer BL, Pasternak JF. 1990. NMDA receptor antagonists inhibit kindling epileptogenesis and seizure expression in developing rats. *Brain Res Dev Brain Res* 53:248–52.
16. Platt SR. 2001. The role of glutamate in neurologic diseases. *Proc 19th Annu Meeting ACVIM*, 427–30.
17. Borris DJ, Bertram EH, Kapur J. 2000. Ketamine controls prolonged status epilepticus. *Epilepsy Res* 42:117–22.
18. Szakacs R, Weiczner R, Mihaly A, *et al*. 2003. Non-competitive NMDA receptor antagonists moderate seizure-induced c-fos expression in the rat cerebral cortex. *Brain Res Bull* 59:485–93.
19. Working group on status epilepticus. 1993. Treatment of convulsive status epilepticus: recommendations of the epilepsy foundation of Americas working group on status epilepticus. *J Am Med Assoc* 270:854–59.
20. Mayhew IG. 1998. When should I start anticonvulsant therapy for a mature epileptic horse, and what medication should I use? *Compend Contin Educ Pract Vet* 20:744–6.
21. Mayhew IGJ. 2003. Rules of thumb in managing epileptic horses. In *The North American Veterinary Conference 2003, Large Animal*, 172–3. Gainesville: North American Veterinary Conference.
22. Podell M. 1996. Seizures in dogs. *Vet Clin North Am Small Anim Pract* 26:779–809.
23. Ravis WR, Duran SH, Pedersoli WM, *et al*. 1987. A pharmacokinetic study of phenobarbital in mature horses after oral dosing. *J Vet Pharmacol Ther* 10:283–9.
24. Knox DA, Ravis WR, Pedersoli WM, *et al*. 1992. Pharmacokinetics of phenobarbital in horses after single and repeated oral administration of the drug. *Am J Vet Res* 53:706–10.
25. Duran SH, Ravis WR, Pedersoli WM, *et al*. 1987. Pharmacokinetics of phenobarbital in the horse. *Am J Vet Res* 48:807–10.
26. Spehar AM, Hill MR, Mayhew IG, *et al*. 1984. Preliminary study on the pharmacokinetics of phenobarbital in the neonatal foal. *Equine Vet J* 16:368–71.
27. Magdesian KG. 2002. Neonatal pharmacology and therapeutics. In *Current Therapy in Equine Medicine 5*, edited by Robinson NE, 1–5. Philadelphia:Saunders.
28. LeBlanc PH, Brunson DB. 1986. Anesthetic management of equine head trauma: a case report. *Vet Surg* 15:279–82.
29. Wilkins PA. 2003. Hypoxic ischemic encephalopathy: neonatal encephalopathy. In *Recent Advances in Equine Neonatal Care*, edited by Wilkins PA,

Palmer JE. Ithaca:International Veterinary Information Service.
30. Mayhew IG. 1989. Seizures. In *Large Animal Neurology: a Handbook for Veterinary Clinicians*, edited by Mayhew IG, 113–25. Philadelphia: Lea&Febiger.
31. Raidal SL, Edwards S. 2005. Pharmacokinetics of potassium bromide in adult horses. *Aust Vet J* 83:425–30.
32. Fielding CL, Magdesian KG, Elliott DA, *et al*. 2003. Pharmacokinetics and clinical utility of sodium bromide (NaBr) as an estimator of extracellular fluid volume in horses. *J Vet Intern Med* 17:213–7.
33. Trepanier LA, Van Schoick A, Schwark WS, *et al*. 1998. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992–1996). *J Am Vet Med Assoc* 213:1449–53.
34. Yohn SE, Morrison WB, Sharp PE. 1992. Bromide toxicosis (bromism) in a dog treated with potassium bromide for refractory seizures. *J Am Vet Med Assoc* 201:468–70.
35. Knight HD, Costner GC. 1977. Bromide intoxication of horses, goats, and cattle. *J Am Vet Med Assoc* 171:446–8.
36. Kowalczyk DF, Beech J. 1983. Pharmacokinetics of phenytoin (diphenylhydantoin) in horses. *J Vet Pharmacol Ther* 6:133–40.
37. Sihna AK, Cox JH. 1995. Diseases of the brain. In *The Horse: Diseases and Clinical Management*, edited by Kobluk CN, Ames TR, Geor RJ, 413–41. Philadelphia: W.B. Saunders Co.
38. May CJ, Greenwood RE. 1977. Recurrent convulsions in a thoroughbred foal: management and treatment. *Vet Rec* 101:76–7.
39. Blakely AA. 1962. Diseases of foals. *NZ Vet J* 10:79–85.
40. Podell M. 2001. Strategies of antiepileptic drug therapy. In *Proc 19th Annu Meeting ACVIM*, 430–1.
41. Berendt M, Høgoenhaven H, Flagstad A, *et al*. 1999. Electroencephalography in dogs with epilepsy: Similarities between human and canine findings. *Acta Neurol Scand* 99:276–83.
42. Jaggy A, Bernardini M. 1998. Idiopathic epilepsy in 125 dogs: A long-term study. Clinical and electroencephalographic findings. *J Small Anim Pract* 39:23–9.
43. Kube SA, Aleman M, Williams DC, *et al*. 2004. How to work up a horse with seizures. *Proc Annu Meeting Am Assoc Equine Pract* 50:418–24.
44. Hubbell JA, Hinchcliff KW, Grosenbaugh DA, *et al*. 2002. Ureteral ligation prevents the haemodynamic effect of frusemide in pentobarbitol anaesthetised horses. *Equine Vet J* 34:580–6.
45. Mackay RJ. 2004. Brain injury after head trauma: pathophysiology, diagnosis, and treatment. *Vet Clin North Am Equine Pract* 20:199–216.
46. Hines MT. 2003. Changes in mentation, seizures and narcolepsy. In *Current Therapy in Equine Medicine 5*, edited by Robinson NE, 764–71. Philadelphia: Saunders.
47. Odio CM, Faingezicht I, Paris M, *et al*. 1991. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med* 324:1525–31.
48. Brayton CF. 1986. Dimethyl sulfoxide (DMSO): a review. *Cornell Vet* 76:61–90.
49. Blythe LL, Craig AM, Christensen JM, *et al*. 1986. Pharmacokinetic disposition of dimethyl sulfoxide administered intravenously to horses. *Am J Vet Res* 47:1739–43.
50. Del Bigio M, James HE, Camp PE, *et al*. 1982. Acute dimethyl sulfoxide therapy in brain edema. Part 3: effect of a 3-hour infusion. *Neurosurgery* 10:86–9.
51. Tan S, Parks DA. 1999. Preserving brain function during neonatal asphyxia. *Clin Perinatol* 26:733–47.
52. Galvin N, Collins D. 2004. Perinatal asphyxia in the foal: review and case report. *Irish Vet J* 57: 707–14.
53. Slovis NM. 2003. Perinatal asphyxia syndrome (hypoxic ischemic encephalopathy). *Proc 21st Annu Meeting ACVIM*, 250–1.
54. Eades S, Waguespack C. 2006. The gastrointestinal and digestive system. In *The Equine Manual*, edited by Higgins AJ, Snyder JR, 529–626. Philadelphia: Saunders.
55. Vaala WE. 2002. Perinatal asphyxia syndrome in foals. In *Current Therapy in Equine Medicine 5*, edited by Robinson NE, 644–9. Philadelphia: Saunders.
56. Sheather AL. 1924. Fainting in foals. *J Comp Pathol* 62:106–13.
57. Sweeney CR, Hendricks JM, Beech J, *et al*. 1984. Narcolepsy in a horse. *J Am Vet Med Assoc* 183:126–8.
58. Dreifuss FE, Flynn DV. 1984. Narcolepsy in a horse. *J Am Vet Med Assoc* 184:131–2 (Letter).
59. Mayhew IG. 1983. Coma and altered states of consciousness. In *Large Animal Neurology*, edited by Mayhew IG, 133–46. Philadelphia:Lea and Febinger.
60. Hines MT, Schott HC, Byrne BA. 1992. Adult-onset narcolepsy in the horse. *Proc Annu Meeting Am Assoc Equine Pract* 38:289–96.

7
Differential Diagnosis of Equine Spinal Ataxia

Martin Furr and Stephen Reed

Spinal ataxia is a common expression of central nervous system (CNS) disease in the horse. The clinical signs that result from many conditions of the equine spinal cord are similar, making a clear-cut diagnosis difficult solely on clinical grounds. Creating order out of the myriad causes of ataxia, in the form of a differential diagnosis list and a diagnostic plan, requires a careful consideration of all pertinent information. Forming a differential diagnosis is the act of bringing together all the historical and physical examination information to construct a list of reasonable disorders that will determine the next step in the diagnostic process. Doing so requires knowledge of the various conditions which can affect the horse, as well as their most common presentations. In addition, a sound neurologic examination with neuroanatomic localization of the lesion is critical in forming the differential diagnosis list and selecting appropriate ancillary tests to make a final diagnosis. In almost all cases of spinal ataxia, a complete evaluation will include, in addition to the physical and neurologic examination, a complete blood cell count, serum biochemistry profile, radiographs of the cervical spine, and a cerebrospinal fluid evaluation. Depending upon the specific presentation, microbial or viral culture, viral antibody titers, *Sarcocystis neurona* testing, or other specific procedures may be required.

A routine physical examination is important as it will help illuminate any other physical abnormalities that may contribute to or be a part of the neurologic problem. In horses that demonstrate hind limb gait deficits, a rectal examination to assess internal iliac artery pulses may be necessary. Palpation of large muscle masses for pain or firmness, joints for distention, and digital pulses to rule out laminitis should be a part of the examination to eliminate these non-neurologic problems which can be confused with nervous system disease.

Results of the physical and neurologic examination allow the clinician to answer a few important questions: (1) are there conclusive signs of nervous system disease, and is it central or peripheral, (2) what is the neuroanatomic localization of the lesion, (3) do the clinical signs arise from a single site, multifocal sites, or diffuse inflammation, and (4) are the clinical signs symmetric or asymmetric?

In animals in which spinal ataxia is the predominant clinical sign, the lesion may arise from either brain, brainstem, or spinal cord. The ataxia associated with focal brain lesions (cranial to the red nucleus) is usually very mild. Focal brainstem lesions result in proprioceptive deficits, variable degrees of ataxia, and some alteration of mentation. Brain and brainstem lesions should also be reflected by changes in the cranial nerve responses as detected from a neurologic examination. In cases in which the ataxia originates from the spinal cord, the mentation will be normal.

From the findings of the neurologic examination, a determination of whether the clinical signs arise from a single site can be made. Conditions that result in a single focus include the compressive diseases (cervical compressive myelopathy, intervertebral disc protrusion, and fracture), while multifocal or diffuse disease is most often associated with conditions such as equine protozoal myeloencephalitis (EPM), verminous myelitis, and polyneuritis equi. In addition, the presence or absence of symmetry can be useful. Cervical compressive myelopathy,

Table 7.1. Comparative Characteristics of Some Common Causes of Equine Spinal Ataxia

	Cervical Vertebral Myelopathy	EHV-1	EPM	LMND	Fracture
History	Chronic, progressive	Acute, progressive	Chronic, progressive	Chronic, progressive	Acute, non-progressive
Symmetrical (yes/no)	Yes	Yes	No	Yes	Variable
UMN/LMN	UMN predominant	Mixed	Mixed/LMN	LMN	Mixed
Muscle atrophy (yes/no)	No	Rare	Yes	Yes	No
Unifocal/Multifocal	Unifocal	Multifocal	Unifocal or multifocal	Diffuse	Unifocal

EHV-1, herpesvirus 1 encephalitis; EPM, equine protozoal myeloencephalitis; LMN, lower motor neuron; UMN, upper motor neuron.

equine degenerative encephalomyelopathy, neuroaxonal dystrophy, and motor neuron disease are typically symmetrical, while EPM, verminous myelopathy, or neoplastic growths are more likely to be asymmetrical. These are generalizations, of course, and an individual case may differ, but they generally hold true (Table 7.1).

The presence of systemic illness is an important finding in horses with neurologic disease. Infectious diseases such as viral encephalitis [equine encephalitis, West Nile virus encephalitis (WNV), equine herpesvirus 1 encephalitis (EHV-1)] usually result in constitutional signs of illness such as fever, depression, and anorexia which may precede or be coincident with the neurologic abnormalities. Vague and non-specific neurologic signs can be seen in horses which are in circulatory shock from any cause, or which have serious electrolyte disturbances. Severe pain associated with colic may make horses tremble uncontrollably and stumble when walking, yet may not demonstrate more classic signs of abdominal pain. Careful examination of such horses is necessary to determine the true nature and extent of their illness (Table 7.2).

Table 7.2. Infectious, Iatrogenic, Idiopathic, and Inflammatory Conditions in Which Spinal Ataxia is a Prominent Component

Viral meningoencephalitis
  Numerous agents
Bacterial meningitis
  Numerous agents
Protozoal myeloencephalitis
  Sarcocystis neurona
  Toxoplasma gondii
  Neospora hughesi
Verminous myelitis
  Numerous agents
Vertebral osteomyelitis
Discospondylitis
Cauda equine neuritis
Fibrocartilagenous embolism[53]
Aortic-iliac thrombosis[54]
Air embolism
Post-anesthetic hemorrhagic myelopathy
Cholesterol granuloma[52]
Intracarotid injection

Signalment includes the horse's breed, age, gender, and use. Certain conditions have been demonstrated to have a breed, age, and gender association, and while this does not confirm a specific condition, it is important information in narrowing the differential diagnosis list. In one study of 100 horses with spinal ataxia Thoroughbred horses were much more commonly affected by cervical compressive myelopathy than any other breed represented in the study.[1] Another report reviewing the cause of ataxia in 19 horses did not demonstrate a clear breed or age predisposition for cervical compressive myelopathy;[2] however, both studies were retrospective surveys and there were strong population biases. It is widely reported, however, that Thoroughbreds and Quarter horses have a higher incidence of cervical compressive myelopathy than

other breeds.[3,4] Clinical experience suggests that various warmblood breeds, which have recently become much more popular in the United States, are also predisposed to the development of cervical compressive myelopathy, but there are no published reports to confirm this. Cerebellar abiotrophy and atlantooccipital malformation are more commonly (but not exclusively) seen in the Arabian, and neuroaxonal dystrophy is seen as a breed-related phenomenon in Morgan horses (Table 7.3).

Age is also an important factor to consider in formulating the differential diagnosis for horses with spinal ataxia. Most horses presented for ataxia are 3 years of age or less, corresponding to the high prevalence of cervical compressive myelopathy in young horses that are of training age.[1,5] Congenital abnormalities are most usually noted at a very young age. Cervical fracture was most commonly noted in horses less than 5 years of age, while lumbar fractures and sacroiliac subluxations and fractures appeared more common in horses over 5 years of age.[1]

The clinical history and progression of the illness is of particular importance in the evaluation of ataxic horses. It is important to proactively question the owner or caretaker and to probe until given precise answers. An acute or rapid onset is often associated with traumatic events; however, it is important to determine whether more subtle signs of ataxia were present prior to an observed fall. Alternately, a fall or other traumatic event may worsen a pre-existing but less severe condition. Cervical compressive myelopathy is most often slowly progressive and may have a mild waxing and waning course, or rarely a sudden worsening. A similar history is most often observed in horses with EPM, although clinical signs in horses with EPM can progress rapidly in a small number of cases. The clinical signs associated with equine degenerative myeloencephalopathy are reported to progress moderately rapidly after they are first observed. Infectious diseases such as eastern or western encephalitis, rabies, or WNV usually are observed to have a rapid progression, with clinical signs observed to worsen quickly for a few days, then stabilize.

A history of recent medications is important to note, as various anthelmintics and tranquilizers have been noted to result in CNS disease. The type of feed and forage should be noted, as ataxia has been observed in horses which consumed sorghum, and a variety of ataxia syndromes have been described in horses grazing various grasses.

As most horses are fastidious eaters, toxicity syndromes appear to be fairly rare in the horse, but a rather bewildering variety of toxins have been reported in the horse. While most horses will avoid

Table 7.3. Developmental/degenerative Conditions in which Spinal Ataxia is a Prominent Component

Cerebellar abiotrophy[28]
Atlantoaxial malformations[29]
Focal compression
Cervical compressive myelopathy[1,2]
Tumors (see Table 7.5)
Intervertebral disk prolapse[30,31]
Cervical arthritis[32]
Vascular malformations[33]
Synovial cysts[34]
Arachnoid diveticulum[35]
Cleft vertebral column[36]

Table 7.4. Selected Toxic Agents in which Spinal Ataxia is a Prominent Component

Stinging nettles[6]
Onion Weed (*Trachyandra divaricata*)[7]
Topical amitraz[8]
Amprolium[9]
Sorghum–associated (lolitrem B)[10,11]
Moxidectin[13]
Ivermectin[14]
Crotalaria[15]
Propylene glycol[16,17]
Ionophores
Monensin[18]
Lasalocid
Salinomycin[19]
Pipothiazine[20]
Fluphenazine[21,22]
Tremetol[23]
Heavy metals
Lead[24]
Arsenic[25]
Bromide[26]
Moldy corn[27]
Lathyrism
Swainsonia poisoning[12]
Locoism

Table 7.5. Specific Neoplastic Conditions Reported in the Horse in which Spinal Ataxia has been noted as a prominent Component

Plasma cell myeloma[37]
Undifferentiated sarcoma[38]
Melanoma[39]
Pheochromocytoma[40]
Squamous cell carcinoma[41]
Lymphoma/lymphosarcoma[42,43]
Angioma[44]
Hemartomas
Ependymoma[45]
Hemangiosarcoma[46]
Angiosarcoma[49]
Meningioangiomatosis[47]
Oligodendroglioma[48]
Choroid plexus papilloma[50]
Metastatic intestinal adenocarcinoma[51]

toxic plants, horses which are starving on a grossly overgrazed pasture may be forced to consume plants that they would otherwise avoid. Hence, examining the horse's housing may be useful. Many intoxications of the horse lead to generalized neurologic signs (trembling, seizures, and mentation changes), while few are associated with spinal ataxia alone. These include Rye grass associated ataxia, Dallis grass ataxia, and sorghum-associated ataxia/cystitis. Non-specific neurologic sign noted in horses with many forms of intoxication may be related to specific neurologic damage, as well as to non-specific changes such as dehydration, alteration in blood pressure, or electrolyte disorders, underscoring the importance of a complete evaluation (Tables 7.4, 7.5).

Once a differential list is constructed, the clinician will use it to direct further evaluation and determine ancillary testing which may be needed. Additional testing may include imaging, clinical chemistry analysis, myelography, electrodiagnostic testing, or collection and assay of various biological fluids or feed samples.

REFERENCES

1. Reed S, Bayly W, Traub JL, *et al*. 1981. Ataxia and paresis in horses Part 1. Differential diagnosis. *Compend Contin Educ Pract Vet* 3:S88–98.
2. Nappert G, Vrins A, Breton L, *et al*. 1989. A retrospective study of nineteen ataxic horses. *Can Vet J* 30:802–6.
3. Mayhew IG, DeLahunta A, Whitlock RH. 1978. History and clinical evaluation [of spinal cord disease in horses]. *Cornell Vet Suppl* 68:24–35.
4. Mayhew IJ. 1989. Neurologic evaluation. In *Large Animal Neurology*, edited by Mayhew IG, 15–47. Philadelphia:Lea and Febinger.
5. Smith JM, Cox JH. 1987. Central nervous system disease in adult horses. II. Differential diagnosis. *Compend Contin Educ Pract Vet* 9:772–8.
6. Bathe AP. 1994. An unusual manifestation of nettle rash in three horses. *Vet Rec* 134:11–2.
7. Huxtable CR, Chapman HM, Main DC, *et al*. 1987. Neurological disease and lipofuscinosis in horses and sheep grazing *Trachyandra divaricata* (branched onion weed) in south Western Australia. *Aust Vet J* 64:105–8.
8. Auer DE, Seawright AA, Pollitt CC, *et al*. 1984. Illness in horses following spraying with amitraz. *Aust Vet J* 61:257–9.
9. Cymbaluk NF, Fretz PB, Loew FM. 1978. Amprolium-induced thiamine deficiency in horses: clinical features. *Am J Vet Res* 39:255–61.
10. Adams LG, Dollahite JW, Romane WM, *et al*. 1969. Cystitis and ataxia associated with sorghum ingestion by horses. *J Am Vet Med Assoc* 155:518–24.
11. Sloet van Oldruitenborgh-Oosterbaan MM, Schipper FC, Goehring LS, *et al*. 1999. [Rhinopneumonia or mycotoxin intoxication? Neurologic phenomena in horses from a riding school]. *Tijdschr Diergeneeskd* 124:679–81.
12. van Essen GJ, Blom M, Fink Gremmels-Gehrmann J. 1995. [Ryegrass cramps in horses]. *Tijdschr Diergeneeskd* 120:710–1.
13. Khan SA, Kuster DA, Hansen SR. 2002. A review of moxidectin overdose cases in equines from 1998 through 2000. *Vet Hum Toxicol* 44:232–5.
14. Hautekeete LA, Khan SA, Hales WS. 1998. Ivermectin toxicosis in a zebra. *Vet Hum Toxicol* 40: 29–31.
15. Arzt J, Mount ME. 1999. Hepatotoxicity associated with pyrrolizidine alkaloid (*Crotalaria* spp.) ingestion in a horse on Easter Island. *Vet Hum Toxicol* 41:96–9.
16. McClanahan S, Hunter J, Murphy M, *et al*. 1998. Propylene glycol toxicosis in a mare. *Vet Hum Toxicol* 40:294–6.
17. Dorman DC, Haschek WM. 1991. Fatal propylene glycol toxicosis in a horse. *J Am Vet Med Assoc* 198:1643–4.
18. Matsuoka T. 1976. Evaluation of monensin toxicity in the horse. *J Am Vet Med Assoc* 169:1098–100.
19. Rollinson J, Taylor FG, Chesney J. 1987. Salinomycin poisoning in horses. *Vet Rec* 121:126–8.
20. McCrindle CM, Ebedes H, Swan GE. 1989. The use of long-acting neuroleptics, perphenazine enanthate

and pipothiazine palmitate in two horses. *J S Afr Vet Assoc* 60:208–9.
21. Kauffman VG, Soma L, Divers TJ, *et al*. 1989. Extrapyramidal side effects caused by fluphenazine decanoate in a horse. *J Am Vet Med Assoc* 195:1128–30.
22. Brewer B, Hines M, Stewart JT, *et al*. 1990. Fluphenazine induced parkinson-like syndrome in a horse. *Equine Vet J* 22:136–7.
23. Olson CT, Keller WC, Gerken DF, *et al*. 1984. Suspected tremetol poisoning in horses. *J Am Vet Med Assoc* 185:1001–3.
24. Sojka JE, Hope W, Pearson D. 1996. Lead toxicosis in 2 horses: similarity to equine degenerative lower motor neuron disease. *J Vet Intern Med* 10:420–3.
25. Pace LW, Turnquist SE, Casteel SW, *et al*. 1997. Acute arsenic toxicosis in five horses. *Vet Pathol* 34:160–4.
26. Knight HD, Costner GC. 1977. Bromide intoxication of horses, goats, and cattle. *J Am Vet Med Assoc* 171:446–8.
27. McCue P. 1989. Equine leukoencephalomalacia. *Compend Contin Educ Pract Vet* 11:646–51.
28. Baird JD, Mackenzie CD. 1974. Cerebellar hypoplasia and degeneration in part-Arab horses. *Aust Vet J* 50:25–8.
29. Mayhew IG, Watson AG, Heissan JA. 1978. Congenital occipitoatlantoaxial malformations in the horse. *Equine Vet J* 10:103–13.
30. Furr MO, Anver M, Wise M. 1991. Intervertebral disk prolapse and diskospondylitis in a horse. *J Am Vet Med Assoc* 198:2095–6.
31. Jansson N. 2001. What is your diagnosis? Multiple cervical intervertebral disk prolapses. *J Am Vet Med Assoc* 219:1681–2.
32. von Schebitz H, Schulz LC. 1965. [On the pathogenesis of spinal ataxia in horses – spondylarthrosis, clinical findings]. *Dtsch Tierarztl Wochenschr* 72:496–501.
33. Gilmour JS, Fraser JA. 1977. Ataxia in a Welsh cob filly due to a venous malformation in the thoracic spinal cord. *Equine Vet J* 9:40–2.
34. Fisher LF, Bowman KF, MacHarg MA. 1981. Spinal ataxia in a horse caused by a synovial cyst. *Vet Pathol* 18:407–10.
35. Allison N, Moeller RB, Jr. 2000. Spinal ataxia in a horse caused by an arachnoid diverticulum (cyst). *J Vet Diagn Invest* 12:279–81.
36. Doige CE. 1996. Congenital cleft vertebral centrum and intra- and extraspinal cyst in a foal. *Vet Pathol* 33:87–9.
37. Edwards DF, Parker JW, Wilkinson JE, *et al*. 1993. Plasma cell myeloma in the horse. A case report and literature review. *J Vet Intern Med* 7:169–76.
38. Van Biervliet J, Alcaraz A, Jackson CA, *et al*. 2004. Extradural undifferentiated sarcoma causing spinal cord compression in 2 horses. *J Vet Intern Med* 18:248–51.
39. Traver DS, Moore JN, Thornburg LP, *et al*. 1977. Epidural melanoma causing posterior paresis in a Horse. *J Am Vet Med Assoc* 170:1400–3.
40. Johnson PJ, Goetz TE, Foreman JH, *et al*. 1995. Pheochromocytoma in two horses. *J Am Vet Med Assoc* 206:837–41.
41. Patterson LJ, May SA, Baker JR. 1990. Skeletal metastasis of a penile squamous cell carcinoma. *Vet Rec* 126:579–80.
42. Kannegieter NJ, Alley MR. 1987. Ataxia due to lymphosarcoma in a young horse. *Aust Vet J* 64: 377–9.
43. Shamis LD, Everitt JI, Baker GJ. 1984. Lymphosarcoma as the cause of ataxia in a horse. *J Am Vet Med Assoc* 184:1517–8.
44. Palmer AC, Hickman J. 1960. Ataxia in a horse due to an angioma of the spinal cord. *Vet Rec* 72: 611–3.
45. Huxtable CR. 2000. Marginal siderosis and degenerative myelopathy: a manifestation of chronic subarachnoid hemorrhage in a horse with myxopapillary ependymoma. *Vet Pathol* 37: 483–5.
46. Berry S. 1999. Spinal cord compression secondary to hemangiosarcoma in a saddlebred stallion. *Can Vet J* 40:886–7.
47. Frazier K, Liggett A, Hines M, *et al*. 2000. Mushroom toxicity in a horse with meningioangiomatosis. *Vet Hum Toxicol* 42:166–7.
48. Reppas GP, Harper CG. 1996. Sudden unexpected death in a horse due to a cerebral oligodendroglioma. *Equine Vet J* 28:163–5.
49. Haghdoost IS, Zakarian B. 1985. Neoplasms of equidae in Iran. *Equine Vet J* 17:237–9.
50. Pirie RS, Mayhew IG, Clark CJ, *et al*. 1998. Ultrasonographic confirmation of a space-occupying lesion in the brain of a horse: choroid plexus papilloma. *Equine Vet J* 30:445–8.
51. Spoormakers TJP, Ijzer J, van Oldruitenborgh-Oosterbaan S. 2000. Neurologic signs in a horse due to metastases of an intestinal adenocarcinoma. *Vet Q* 23:49–50.
52. de Lahunta A, Jefferson DA, Geary JC, *et al*. 1969. Granuloma compressing the brain of a pony. *Cornell Vet* 59:622–39.
53. Taylor HW, Vandevelde M, Firth EC. 1977. Ischemic myelopathy caused by fibrocartilaginous emboli in a horse. *Vet Pathol* 14:479–81.
54. Mayhew IG, Kryger MD. 1975. Aortic-iliac-femoral thrombosis in a horse. *VM SAC Vet Med Small Anim Clin* 70:1281–4.

8
Differential Diagnosis and Management of Cranial Nerve Abnormalities

Bonnie Rush, Laurie Beard, and Martin Furr

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF VESTIBULAR DISEASE

Bonnie Rush

The vestibular system is a special proprioceptive system responsible for the maintenance of balance and reflex orientation to gravitational forces. This system functions to maintain appropriate eye, trunk, and limb position in reference to movements and positioning of the head. The vestibular system is comprised of the inner ear, vestibular portion of the vestibulocochlear nerve (cranial nerve (CN) VIII), and vestibular nuclei in the brainstem. From the vestibular nuclei, projections go to the cerebellum, extraocular muscle nuclei, antigravity muscles, and opposite vestibular nuclei. The overall response is a coordinated muscle response to maintain balance, and produce smooth, coordinated movements.

Clinical signs of acute vestibular dysfunction include head tilt, nystagmus, falling, circling, reluctance to move, and asymmetric ataxia with preservation of strength.[1] Horses affected with peracute vestibular disease are often violent due to disorientation. A true head tilt is a consistent sign of vestibular disease and is characterized by ventral deviation of the poll of the head toward the affected side (see Figure 8.1). Affected horses prefer to lie on the side of the lesion and may lean on the wall toward the affected side when standing. When forced to move, the horse will take short, uncoordinated steps in a circle toward the direction of the lesion. The body may be flexed laterally with a concavity toward the lesion. Extensor hypotonia ipsilateral to the lesion and mild hypertonia and hyperreflexia of the extensor muscles of the contralateral side results in asymmetric ataxia. Extensor hypotonia occurs due to loss or dysfunction of facilitatory neurons of the vestibulospinal tract to ipsilateral extensor muscles. Contralateral extensor hypertonia occurs due to loss or dysfunction of inhibitory neurons and unopposed extensor tone of the contralateral vestibulospinal tract.

Pathologic nystagmus is involuntary, rhythmic oscillations of the eyes occurring while the head is in a stationary position and is indicative of a lesion in either the vestibular system or cerebellum. As in physiologic nystagmus (Doll's eye response), a fast and slow phase is identified. Nystagmus may be horizontal, vertical, or rotary. The directions of horizontal and vertical nystagmus are defined by the direction of the fast phase (left/right, ventral/dorsal). The direction of rotary nystagmus is defined by the direction the limbus moves from the twelve o'clock position (clockwise or counterclockwise) during the fast phase. Pathologic nystagmus may be spontaneous, occurring with the head in the resting position, or positional which is induced by elevation or lateral flexion of the head. Many horses blink during the fast phase, which may hinder detection of nystagmus.

Ventrolateral strabismus is often observed ipsilateral to the vestibular lesion and is ideally demonstrated by elevation of the head and extension of the neck (see Figure 8.2). Mild ventral deviation of the eyes is observed in normal horses when the head is elevated, but it is a symmetric finding. CN VIII does



Figure 8.1. Left-sided head tilt and facial nerve paralysis in an 8-yr old Quarter Horse gelding due to temporohyoid osteoarthropathy.



Figure 8.2. Ventrolateral strabismus resulting from right-sided peripheral vestibular dysfunction in an 11-yr old Quarter Horse gelding. Note the abnormality is demonstrated by elevating the muzzle.

not directly control any extraocular muscle. Rather, ventrolateral strabismus associated with vestibular dysfunction results from abnormal upper motor neuron input on the oculomotor nucleus from ipsilateral vestibular nucleus via the medial longitudinal fasciculus.

Ataxia and dysmetria are often severe with vestibular dysfunction; however, strength is maintained. Postural reactions will remain normal, with the exception of the righting reflex. The motor system is unable to accurately control movement and identify the location of different parts of the body at a given time. Therefore, an exaggerated response will be made toward the side of the lesion as the horse attempts to stand.

Facial nerve (CN VII) paralysis frequently occurs concurrently with vestibular disease due to the proximity of the facial nerve to the vestibular nerve within the petrous temporal bone and the proximity of the facial and vestibular nuclei in the medulla. Paresis or paralysis of the facial nerve produces muzzle deviation away from the affected side, absent menace response, absent palpebral response, ear droop, decreased nostril flare, and buccal impaction of feed. Keratitis and corneal ulceration are common complications of facial nerve paralysis due to inability to blink and decreased tear production. Decreased tear production results from damage to parasympathetic fibers to the lacrimal gland, which travel with the facial nerve to the eye. With chronicity, some horses learn to retract the globe allowing the eyelid and nictitating membrane to slide across the surface of the cornea, to distribute lubrication and protect the cornea from trauma.

Differentiation of central versus peripheral vestibular disease is important for establishing a

list of differential diagnoses, initiating therapy, and formulating a prognosis.[2] A thorough examination may identify nonvestibular neurologic signs that provide additional information regarding lesion location. The duration of vestibular signs, rate of onset, and disease progression may aid in differentiation of central from peripheral vestibular disease.

Peripheral vestibular dysfunction produces horizontal nystagmus, with the fast phase directed away from the lesion. The direction of nystagmus will not change with changing head position. Central vestibular dysfunction can product horizontal, rotary, or vertical nystagmus, and the type of nystagmus may change with head position. Often, the fast phase is directed away from the central lesion, but this is not a consistent finding.

The onset of vestibular signs in a horse with an expanding space-occupying central lesion will not be as dramatic as peripheral nerve damage; adjustments by compensatory mechanisms occur during slow development of the lesion. These lesions, however, are not likely to show significant clinical improvement after the onset of clinical signs, as may occur with peripheral vestibular lesions.

If vestibular signs are accompanied by depression, weakness, seizure, or conscious proprioceptive deficits, a central vestibular system lesion should be suspected. The nuclei of the trigeminal (CN V) and the abducens nerve (CN VI) are in anatomic proximity to the vestibular nuclei and are readily damaged in a common disease process. In some instances, limb weakness and proprioceptive deficits are observed on the side of the body opposite to the direction of the head tilt, termed paradoxical vestibular syndrome. When this occurs, the neuroanatomic localization is likely at the cerebellopontine angle, ipsilateral to the hemiparesis (Table 8.1).

Signs of vestibular disease may improve 2 to 3 weeks after onset due to visual and central accommodation. Central vestibular lesions are slower to compensate than peripheral vestibular lesions; signs may even progress if the central lesion is an expanding space-occupying mass. Human vestibular patients compensate satisfactorily for unilateral disease but are not required to be coordinated athletes performing at high speed. Blindfolding a horse with compensated disease will result in ataxia and a head tilt (Romberg test). Blindfolding eliminates visual and limb proprioceptive orientation; the body is forced to rely on the impaired vestibular system for equilibrium. Horses may dramatically decompensate when the blindfold is placed over the eyes, resulting in anxiety, disorientation, and falling. The test should be performed with caution on a padded surface with good footing.

Table 8.1. Neurologic Causes of Head Tilt in the Horse

Skull fractures
Temporohyoid osteoarthropathy
Equine protozoal myeloencephalopathy
Otitis media/interna
Intracranial abscess
Basilar empyema
Central nervous system neoplasia
Viral encephalitis
Verminous encephalitis
Lightning strike
Listeriosis (very rare in horses)
Streptomycin
Polyneuritis equi

Vestibular disease may result from a number of infectious, traumatic, and non-infectious conditions.[2] Temporohyoid osteoarthropathy and head trauma are the most common causes of vestibular disease in horses. Equine protozoal myelitis, neoplasia, brain abscess, West Nile virus, eastern equine encephalitis, and parasitic migration are all potential causes of central-origin vestibular disease in horses.[3–5] Concurrent neurologic signs, cerebrospinal fluid (CSF) analysis, specific antibody testing, and computed tomography (CT) may be able to distinguish between these less common causes of vestibular dysfunction.

Temporohyoid Osteoarthropathy

Temporohyoid osteoarthropathy is the most common cause of peripheral vestibular disease in horses.[6–10] This condition should be a primary differential in all horses with acute onset of vestibular dysfunction, with or without ipsilateral facial nerve paralysis. The onset of neurologic dysfunction in horses with temporohyoid osteoarthropathy represents an acute manifestation of a chronic, proliferative process involving the bones surrounding the inner ear, particularly the stylohyoid and petrous temporal bones. It is unclear whether the bony proliferation results from trauma, infection (otitis

media), or nonseptic degenerative arthrosis due to mechanical stress on the joint.[7,8–10] This condition is observed in adult horses with no breed or gender predilection.

Affected horses have bony proliferation of the tympanic bulla and proximal stylohyoid bone, which results in ankylosis of the temporohyoid joint. The hyoid apparatus is linked in series to the tongue and larynx; fusion of the temporohyoid joint results in impaired flexibility of the unit. Chronic fracture and/or remodeling of stylohyoid bone results from abnormal forces exerted during eating or vocalization due to normal tongue movement. These horses eventually develop a pathologic fracture of the petrous temporal bone, which is evidenced by acute-onset vestibular disease with or without facial nerve paralysis. Some horses develop clinical signs after a routine dental float, chewing hard feeds, or a period of vocalization. Some horses have bilateral arthrosis; however, neurologic signs associated with fracture are typically unilateral.

Neurologic signs are not apparent during formation of proliferative osteitis and temporohyoid joint fusion. Some horses have a history of ear rubbing, head tossing, performance problems, or pain on palpation of the ear in the weeks or months prior to the onset of vestibular dysfunction.[11] The fracture line extends into the cranial vault at the level of the internal auditory meatus resulting in direct trauma to vestibulocochlear and facial nerves and hemorrhage into the middle and inner ear. Given that the fracture extends through the internal acoustic meatus, it may allow secondary contamination of neural structures resulting in focal suppurative meningitis at the level of the pons resulting in fever and depression. Some horses may leak CSF from their external ear on the affected side. Evidence of sepsis at the time of fracture is occasionally observed (consistent with otitis media), but it is not a universal finding. Secondary meningitis complicates treatment and worsens the prognosis for recovery.

Facial nerve paralysis is commonly observed in horses with temporohyoid osteoarthropathy, characterized by ptosis, muzzle deviation away from the affected side, dropped lower lip, and ear droop. Clinical signs of facial nerve paralysis may precede vestibular signs or may not appear for several days after the onset of vestibular disease.[7] Damage to either nerve may be the result of hematoma, callus, infection, or direct laceration by fracture fragments. Corneal ulceration is common in affected horses due to inability to blink and reduced tear production. Preganglionic parasympathetic fibers in the facial nerve that innervate the main lacrimal gland may be damaged resulting in keratoconjunctivitis sicca.

Dysphagia may result from difficult prehension (CN VII), pain associated with the fracture, feed impaction in the buccal pouch (CN VII), or damage to the glossopharyngeal and vagus nerve. Occasionally, the fracture extends to the foramen lacerum, caudal to the petrous temporal bone, where the glossopharyngeal (CN IX) and vagal (CN X) nerves exit the skull. Dysphagia is typically temporary and resolves within a few days.

Diagnosis is usually confirmed by endoscopic examination of the guttural pouch. Osseous proliferation of the proximal stylohyoid bone can be seen at the level of the temporohyoid joint (see Figure 8.3). In some instances, the entire stylohyoid bone is proliferative. Endoscopic examination is more sensitive than radiographic examination for detection of osseous proliferation. Radiographic findings of the lateral and ventrodorsal projections of the skull reveal sclerosis of the tympanic bulla and proximal portion of the stylohyoid bone (see Figure 8.4). It is difficult to identify the actual fracture due to overlapping structures and minimal displacement of

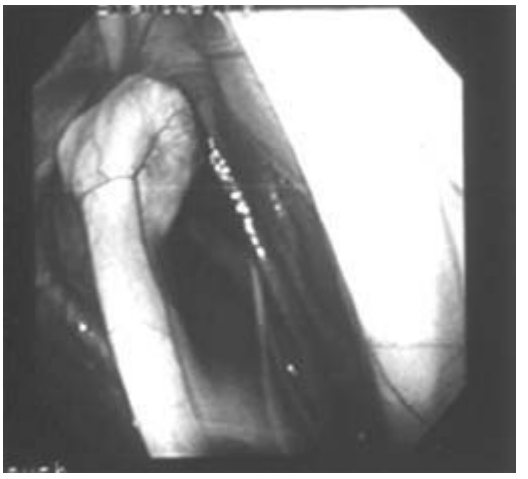


Figure 8.3. Endoscopic examination of the right guttural pouch identifying proliferation of the proximal stylohyoid bone in a horse with temporohyoid osteoarthropathy.



Figure 8.4. Ventrodorsal radiographic projection. Note the increase in bony proliferation of the petrous temporal region on the right side of the radiograph.



Figure 8.5. Computed tomographic image demonstrating proliferative osteitis of the stylohyoid bone (courtesy Dr. S Reed).

fracture fragments. A series of lateral oblique projections may allow visualization of the fracture line. In some instances, CT (see Figure 8.5) or magnetic resonance imaging may be necessary to detect bony proliferation and fracture.[7,9]

Medical therapy for temporohyoid osteoarthropathy includes broad-spectrum antibiotic therapy to prevent meningitis and treat primary or secondary otitis-media interna. Potentiated sulfa antimicrobials, ampicillin (2 mg/kg, IM, q 12 h or q 8 h), and chloramphenicol (15–25 mg/kg PO, q 6 h) have been recommended when culture and sensitivity cannot be obtained. Enrofloxacin should be used due to central nervous system (CNS) irritability and seizure potential with a break in the blood–brain barrier. Nonsteroidal antiinflammatory drugs, such as phenylbutazone (2–4 mg/kg, PO, q 12 h) or flunixin meglumine (500 mg, q 12 h), should be administered to reduce inflammation and pain. Corticosteroid therapy should be considered on a case by case basis.

Horses with facial nerve paralysis are particularly prone to corneal ulceration.[9] A Schirmer's tear test can confirm reduced tear production. Triple antibiotic ophthalmic ointment and artificial tears are indicated q 4–6 h to prevent corneal ulcers. Corneal ulcers progress quickly and heal slowly in these cases, which warrants aggressive (q 2 h) topical treatment in horses that have already developed corneal ulceration. Partial tarsorrhaphy should be performed to prevent or treat corneal ulceration associated with keratoconjunctivitis sicca. Ophthalmic preparations with corticosteroids are contraindicated.

Supportive care, including provision of a padded stall, light sedation, and intravenous fluid therapy, may be necessary in some cases. Affected horses should be offered soft feeds to minimize pain and prevent further displacement of fracture fragments; hard feedstuffs (i.e., cracked corn) should be avoided.

The first surgical procedure described for treatment of temporohyoid osteoarthropathy was the partial stylohyoid ostectomy.[11] This procedure involved

surgical removal of a 2-cm midshaft segment of the stylohyoid bone to dissipate forces generated by the hyoid apparatus during lingual and laryngeal movement. The stylohyoid bone has been observed to heal (reconnect) within months of partial stylohyoid ostectomy, negating the beneficial effects.[12]

An alternative surgical approach has been developed in which the entire ceratohyoid bone is removed.[9] Similar to partial stylohyoid ostectomy, ceratohyoidectomy alleviates mechanical stress on the fused temporohyoid joint. This procedure is technically easier with fewer short-term (hemorrhage/nerve damage) and long-term (regrowth) complications. Neither surgical approach has been evaluated in a case-controlled manner; however, anecdotal reports indicate that surgical intervention improves recovery. Surgical intervention could be performed prior to the onset of neurologic signs in horses with head tossing or ear rubbing that have been identified with stylohyoid osteitis.

The clinical signs of vestibular dysfunction are most severe at the time of fracture. Circling, disorientation, and nystagmus will resolve over the days to weeks following the fracture due to visual compensation. The Romberg test (blindfolding) should be cautiously performed in horses recovering from vestibular disease. The purpose of the test is to differentiate improvement in vestibulocochlear nerve function from compensation due to visual input. Although improvement occurs over time, a subtle head tilt persists in most cases. More than half of surviving horses can return to some athletic ability, although most will have some residual CN VII or CN VIII deficits.[7] The clinician should not expect proliferation of the stylohyoid bone to resolve after treatment. Facial nerve paralysis may improve, but rarely resolves and may ultimately contribute to the loss of an eye due to chronic corneal ulceration. If no improvement of facial nerve deficits occurs within 3 months after the onset of disease, a poor prognosis is given for recovery of these signs.

Head Trauma

There are two basic types of skull fractures that occur in horses following characteristic traumatic incidents. Fractures of the frontal and parietal bones of the calvarium result from a direct blow to the frontal region or collision with a solid object, and basilar skull fractures occur when horses flip over backward and impact the poll.[13]

Frontal bone fractures, resulting from direct impact, are often open, depressed fractures with direct cerebral laceration and hemorrhage by fracture fragments. Neurologic signs associated with frontal bone fractures reflect cerebral cortical damage and increased intracranial pressure. Contralateral cortical blindness (normal pupillary light reflex) and decreased facial sensation, depression, compulsive wandering toward the affected cerebral hemisphere, and generalized seizures are common in horses with frontal head injuries. Development of anisocoria or mydriasis with slow pupillary light reflexes indicates increasing intracranial pressure and significant risk of caudal cerebral herniation. Loss of consciousness and development of mydriatic, unresponsive pupils indicates that herniation of the occipital lobes under the tentorium cerebelli has occurred.

Basilar skull fractures most commonly involve the basisphenoid, basioccipital, and temporal bones and result from impacting the poll when flipping over backward.[13] Basisphenoid fractures occur at the suture between the basisphenoid and basioccipital bones (see Figure 8.6) and result in compression and hemorrhage of the brainstem. Occipital bone fractures may result from avulsion of the insertion of the rectus capitis ventralis muscle or direct impact. Avulsed occipital bone fragments may be identified superimposed over the guttural pouch on a lateral radiographic view of the skull. Petrous temporal bone fracture may destroy the middle/inner ear, resulting in peripheral vestibular dysfunction and facial nerve paralysis. The basilar artery and venous sinuses are often lacerated, with basilar skull fractures producing massive hemorrhage into the calvarium, guttural pouch, or inner ear.

Following traumatic poll injury, horses may lose consciousness for minutes to hours, and some never regain consciousness. The most common clinical signs observed in horses that regain consciousness are depression, vestibular dysfunction, facial nerve paralysis, tetraparesis, and hemorrhage from the nostrils and ear. Leakage of CSF or hemorrhage from the external ear is presumptive evidence of petrous temporal bone fracture. Epistaxis may result from fracture of the cribiform plate, fracture of the basisphenoid/basioccipital bones, or hemorrhage into the guttural pouch. Basisphenoid fractures may lacerate the basilar artery and can produce massive, life-threatening, hemorrhage into the guttural pouch.



Figure 8.6. Lateral radiographic projection of the skull after a traumatic poll injury. Note the basilar skull fracture (between the basisphenoid and basioccipital bones) including an avulsion fragment overlying the guttural pouch.

Neurologic examination is the most important diagnostic and prognostic tool for evaluation of horses with basilar skull fractures.[14] Bilateral miosis signifies rostral midbrain swelling, whereas unresponsive, bilateral mydriasis is a poor prognostic sign associated with midbrain compression or herniation. The rate and character of respiration should be monitored in patients with abnormal pupil size and symmetry. Changes in the rate of respiration and development of abnormal respiratory patterns indicate increasing intracranial pressure and danger of herniation. The combination of bilateral, unresponsive mydriatic pupil, coma, and erratic respiration is consistent with herniation of the cerebellum through the foramen magnum.

In some instances, a traumatic poll or frontal injury may result in bilateral blindness with mydriatic, unresponsive pupils. This injury results from damage or rupture of the optic nerve or the optic chiasm due to shearing forces by the bony optic canals. A basilar skull fracture does not necessarily accompany this lesion, and no other neurologic signs are observed. The prognosis for recovery of vision is poor.

Skull radiographs are indicated in horses with head trauma to determine the type, location, and displacement of fractures and fracture fragments. Depressed, comminuted fractures of the frontal and parietal bones are readily identified radiographically. Conversely, petrous temporal bone fractures are difficult to see, and multiple oblique views may be necessary to identify a fracture line. In young horses, it is difficult to differentiate a fracture of the basisphenoid–basioccipital suture from the normal physeal growth plate. Absence of an obvious fracture line does not preclude a diagnosis of basilar skull fracture; hemorrhage from the guttural pouch or external ear following a traumatic poll injury is presumptive evidence of a basilar skull fracture.

CSF analysis is unlikely to provide further diagnostic or prognostic information in horses with closed head injuries. Cytologic analysis and culture of CSF may be indicated in horses with open fractures of the calvarium to diagnose secondary bacterial meningitis. Additionally, CSF analysis may provide supportive evidence of CNS trauma in horses with acute onset of undiagnosed neurologic disease. Alterations in CSF analysis consistent with CNS trauma are xanthochromia, high red blood cell counts, high protein concentration, and increased creatine kinase activity. Sudden decreases in pressure while performing an atlanto-occipital CSF tap may precipitate herniation; therefore, CSF should be obtained at the lumbosacral site in horses with suspected head trauma.

The brain is encased in a rigid calvarium; therefore, swelling results in increased intracranial

pressure, decreased cerebral blood flow, and pressure-induced necrosis. Early medical therapy (within 8 h of injury) to prevent edema formation produces a more favorable outcome than does late intervention which must be directed at resolving existing edema and reducing intracranial pressure.[14] Glucocorticoid medications (dexamethasone 0.1–0.2 mg/kg, IV, q 8-12 h) may minimize cerebral edema. In humans, massive doses of methylprednisolone sodium succinate (30 mg/kg IV, followed by 5.4 mg/kg/h for 23 h) administered within 8 h of CNS injury reduces the incidence and severity of residual neurologic deficits. Methylprednisolone administration has not been investigated for treatment of head trauma in horses. Nonsteroidal antiinflammatory drugs have limited efficacy to reduce CNS edema and inflammation; however, their analgesic properties may relieve malaise and reduce depression associated with the pain of a skull or vertebral fracture. Mannitol reduces existing CNS edema via hyperosmolar dehydration and may reduce intracranial pressure within 30 min of administration. Mannitol should not be administered if active intracranial hemorrhage is suspected; leakage of mannitol into the neural parenchyma may draw fluid into the interstitial space and worsen cerebral edema. In cases where intracranial hemorrhage is stable, mannitol (1 g/kg, IV over 20 min) is administered as a 20% solution, two to three times per day. Additional discussion of antiinflammatory medication for CNS injury can be found in Section 1, Chapter 4. Further discussion of the pathophysiology of CNS trauma is presented in Section 3, Chapter 12.

Anticonvulsant therapy (diazepam 15 mg, IV slowly) is effective for controlling focal or intermittent generalized seizures for short periods of time. Although phenobarbital is an effective anticonvulsant in horses, it will produce depression and altered consciousness, impairing the ability to monitor mentation and detect deterioration of neurologic status. Therefore, phenobarbital (5–10 mg/kg, IV) administration should be limited to horses with uncontrollable, generalized seizures that are unresponsive to diazepam. In addition to antiseizure activity, phenobarbital may protect against ischemic damage by decreasing cerebral metabolism and decreasing intracranial pressure. Phenobarbital (10 mg/kg, PO, q 12 h) may be used effectively for prolonged control of generalized seizure activity. Therapeutic peak and trough blood concentrations of phenobarbital should be maintained between 15 and 40 μg/ml. Xylazine can be safely administered without increasing intracranial pressure if the head is not permitted to hang below the level of the heart. Phenothiazine medications reduce the seizure threshold, and administration is contraindicated in horses with head trauma. Further discussion of the management of seizures and anticonvulsant medications is presented in Section 2, Chapter 6.

Broad-spectrum antimicrobial drugs are indicated for basilar skull fractures, petrosal bone fractures, and open frontal bone fractures. Basisphenoid fractures may communicate with the guttural pouch and petrosal fractures potentially communicate externally via the external auditory canal. Although many antimicrobial agents will penetrate the blood–brain barrier during the initial inflammatory process, third-generation cephalosporins readily penetrate the intact blood–brain barrier and maintain high CSF concentrations after inflammation has subsided. Further discussion regarding antibiotic treatment of the CNS is presented in Section 1, Chapter 4.

Surgical therapy is indicated for horses with depressed frontal fractures of the calvarium that penetrate nervous tissue, open fractures that communicate with nervous tissue, and deterioration of neurologic status despite medical therapy. Depressed frontal calvarium fractures are reduced by direct traction or elevation of the fracture fragments. Closed head injuries with nondisplaced fractures are not typically managed surgically unless underlying hemorrhage and edema is severe. The most conservative approach to surgical decompression of the calvarium is to place burr holes in the frontal or parietal bones in a triangular pattern. If burr holes are insufficient to relieve intracranial pressure or remove hemorrhage, the holes can be connected to perform a craniotomy. Basilar skull fractures are inaccessible to direct surgical reduction. However, burr holes over the dorsal calvarium may relieve intracranial pressure and prevent secondary pressure-induced necrosis and ischemia in horses with basilar skull fractures that are unresponsive to medical management.

In general, CNS trauma associated with calvarium fracture has a guarded to grave prognosis. Horses that are comatose and fail to respond to therapy within 36 h are unlikely to recover. Response to medical therapy in 6 to 8 h indicates a favorable prognosis for life; however, the ultimate usefulness

of the horse will not be apparent for many months after injury. During healing, exuberant callus may impinge on nervous tissue and result in deterioration in neurologic status in horses that had initially responded favorably to therapy.

Drug Toxicities

Drug toxicities can result in unilateral or bilateral peripheral vestibular disease and deafness. Degeneration of the hair cells within the peripheral receptor organs of the auditory and vestibular system occurs with prolonged administration of aminoglycoside antibiotics. Early vestibular disease may be reversible or centrally compensated, but loss of auditory function is permanent. Streptomycin preferentially affects the vestibular system, whereas, dihydrostreptomycin, kanamycin, gentamicin, neomycin, and vancomycin are more toxic to the auditory system. Vincristine, a vinca alkaloid, can cause bilateral cochlear nerve damage in humans. Auditory function improves several months after discontinuation of the drug.

Lightning Strike

Lightning strike is reported to cause acute vestibular disease in horses due to degeneration and necrosis of the sensory hair cells of the inner ear. The clinical signs are typically unilateral. Facial nerve paralysis may or may not accompany the vestibular signs. Additional physical findings which support a diagnosis of lightning strike include serosanguinous nasal discharge, epistaxis, anal hemorrhage, and retinal damage. Approximately 90% of lightning strike victims have burn lesions, including burnt skin at the tips of the ears, linear full thickness defects, or feathering burn lines in the hair. Histopathology may reveal hemorrhage and necrosis of the temporal bone, vestibular nerve, and adjacent tissue. Whether the mechanism of damage is electrocution or noise trauma is unknown.

Auditory/Vestibular Diagnostic Testing

The caloric test may aid in the differentiation of central from peripheral vestibular disease. In the normal horse, irrigation of ice cold water (12°) into the external auditory canal for 3–5 min will induce horizontal nystagmus, with the fast phase away from the tested labyrinth. Endolymph closest to the tympanic membrane is cooled, increasing its density. A density gradient is created within the semicircular canal, and the cooled endolymph will sink, causing displacement of the hair cells. Warm water (45°) irrigation of the external auditory canal results in horizontal nystagmus with a fast phase toward the tested labyrinth. The warm water test is less reliable. In a nonfunctional labyrinth, no nystagmus is induced. The test is difficult to perform and not entirely reliable, although it may be a helpful diagnostic aid in the anesthetized or comatose horse.

In most cases, the cochlea will be damaged by trauma or inflammation which destroys the peripheral vestibular receptor organ. Detection of hearing loss may help to differentiate central from peripheral vestibular disease. Brainstem auditory-evoked response (BAER) stimulates the auditory system with a series of clicks.[15–17] Far field potentials of the brainstem auditory components are recorded via cutaneous electrodes and a signal averaging system. The response is a series of evoked potentials which appear on the oscilloscope as a series of five waveforms. In humans, five to seven waveforms are present, and each corresponds to a specific neurologic structure. In the horse, functional loss of the cochlea or CN VIII results in the loss of the entire waveform on the side of injury, and the presence or absence of the waveform can differentiate a central from peripheral vestibular lesion. The test is reliable with sedation and general anesthesia. General anesthesia is not necessary to perform the test; however, sedation is recommended. Auditory brainstem testing is further described in Section 2, Chapter 10.

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF DYSPHAGIA

Laurie Beard

Normal Eating

Normal eating is complex and requires normal anatomy and neurological function. The process of eating can be divided into prehension (the uptake of food into the oral cavity), mastication, deglutition (the act of swallowing), and esophageal transport. Dysphagia (*dys*—difficult and *phagein*—to eat) is defined as difficulty with swallowing; however, some authors have suggested that the term should be applied to any condition characterized by difficulty in eating.[18] Abnormalities of mastication and prehension can look similar to difficult swallowing, and close observation is necessary to discriminate between the different problems. Proper definition of the abnormality can facilitate diagnosis because

difficulties of prehension, mastication, and swallowing all have unique differential diagnoses.

Normal prehension requires lips and incisors to grasp and tear the food. Sensory input is important for successful prehension and requires intact olfactory, optic, and trigeminal nerves, providing smell, sight, and sensation of the rostral oral mucosa and lips. Motor innervation to the tongue and lips are provided by the hypoglossal and facial nerves. Normal prehension also depends on the CNS to coordinate movements of the tongue and the lips.

Mastication requires the tongue and buccal muscles to position and cheek teeth to grind the food. The facial nerve provides motor innervation to the muscles of the nose, cheeks, and lips. The trigeminal nerve is sensory for the teeth, oral and buccal mucus membranes, and motor to the muscles of mastication. Sensation to the tongue is provided by the facial nerve (cranial two-thirds) and the glossopharyngeal nerve (caudal one-third).[19] The hypoglossal nerve provides motor innervation to the tongue.

Normal swallowing is complex and requires a series of well-coordinated steps. Initially, the food is moved to the base of the tongue and formed into a bolus. The bolus is next forced caudally, the oropharynx relaxes, and the soft palate elevates to seal the palatopharyngeal arch and nasopharynx.[20] The bolus next enters the oropharynx, and the hyoid apparatus swings rostrodorsally, drawing the larynx forward. The epiglottis is tipped caudally to prevent food from entering the larynx. Finally, the food bolus is moved by pharyngeal muscle contractions, past the cricopharyngeal sphincter, and into the esophagus.

Branches of the glossopharyngeal, vagus, and hypoglossal nerve provide sensory and motor input that initiate the reflexive contractions to induce swallowing.[19,21] The pharyngeal plexus, located on the dorsal aspect of the pharynx, is composed of the pharyngeal branch of the vagus nerve, the pharyngeal branch of the glossopharyngeal nerve, and sympathetic branches from the cranial cervical ganglion.[22] The glossopharyngeal nerve has been considered the primary nerve responsible for swallowing.[19] The glossopharyngeal nerve provides sensory innervation to the soft palate mucosa, caudal nasopharynx, and the caudal third of the tongue.[19,21] The glossopharyngeal nerve also provides motor innervation to the stylopharyngeus muscle that dilates the pharynx to receive the food bolus, and to some of the pharyngeal constrictor muscles responsible for peristaltic contractions that move food.[21] Recent studies in horses challenge the idea that glossopharyngeal nerve pathology consistently results in dysphagia.[21] Bilateral anesthesia of the glossopharyngeal nerve in normal horses results in collapse of the dorsal pharynx and inspiratory obstruction in exercising horses.[23] However, glossopharyngeal anesthesia does not result in dysphagia or any quantifiable swallowing difficulties in horses.[21] Bilateral anesthesia of the pharyngeal branch of the vagus nerve results in persistent dorsal displacement of the soft palate, and dysphagia in horses.[24,25]

The esophageal phase of swallowing involves transport of the food bolus into the stomach with primary peristaltic waves, which are a continuation of the pharyngeal contractions. The bolus is transported to the caudal esophageal sphincter, which relaxes to allow for the bolus to enter the stomach, and then contracts to prevent esophageal reflux. If reflux does occur, esophageal clearance is achieved by a second set of peristaltic waves. Antiperistalsis is normal in ruminants during eructation and regurgitation, but is not normal in horses. Motor innervation to the striated skeletal muscles of the esophagus includes the pharyngeal and esophageal branches of the vagus nerves. Parasympathetic fibers of the vagus nerve supply the smooth muscle of the distal esophagus. Gastric distension results in constriction of the lower esophageal sphincter by mechanical and vagally induced mechanisms.

Diagnostic Approach to Dysphagia

Difficulties of eating are common in horses. The most common causes of difficulties of eating are not neurological in origin and include dentition problems (resulting in difficulties of mastication) and esophageal obstruction (resulting in difficulties of swallowing). It is therefore important to first rule out anatomic or physical abnormalities resulting in difficulties of eating. Functional disorders resulting in difficulties of eating include neurologic, neuromuscular, and primary muscular diseases. A thorough history, physical examination (including watching the horse eat), and additional diagnostic tests (e.g., endoscopic examination and radiographs) are often required for a diagnosis (Tables 8.2, 8.3).

In performing a physical examination, the clinician should pay close attention to the head and neck. Because rabies is a potential cause of dysphagia, protective measures while performing a careful and thorough physical examination are necessary. The owner or caretaker should be questioned carefully about the

Table 8.2. Neurologic Causes of Dysphagia and Difficulty Eating

Lightning strike
Botulism
Polyneuritis equi
Tetanus
Viral meningitis
Rabies
Verminous meningitis
Leukoencephalomalacia
Nigropallidal encephalomalacia
Lead toxicity
Otitis media
Guttural pouch disease with secondary peripheral neuropathy
Snakebite (elapine snakes)
Cerebral disease
Hepatic encephalopathy
Hyperammonemia
Brainstem tumors
Hypoxic-ischemic encephalopathy

Table 8.3. Non-Neurologic Causes of Dysphagia and Difficulty Eating

Dental disease
Esophageal disease
Megaesophagus
Stricture
Intraluminal obstruction
Diverticula
Fractured jaw
Temporomandibular joint disease
Pharyngeal foreign bodies/masses
Glossitis
Cysts
Hyoid apparatus fracture
Jugular thrombosis with secondary swelling
Persistent right aortic arch
White muscle disease

history of the illness, and the vaccination history should be confirmed. Ideally, all clinicians working on horses should have an adequate rabies antibody titer. A valuable activity is to watch the horse eat. The distinction between difficulties of prehension, mastication, and swallowing can often be made at this time. Horses that expel food when chewing may have specific problems of mastication. Coughing and green nasal discharge (food) indicates difficulties in swallowing or (less commonly) esophageal transport. It is also important to distinguish between problems of eating and anorexia. Horses should be offered different feeds such as hay and grain. Horses may not be able to swallow grain, but still retain the ability to swallow hay or water. In some cases, a "grain test" may be helpful in identifying horses with mild dysphagia. Most horses consume a 250 ml cup of grain within 2 min.[26] Horses that are mildly dysphagic will often consume grain slower than this, have more saliva than normal, and have some grain falling from the horse's lip.[26] Ptyalism without dysphagia may result from ingestion of legume plants (especially second-cutting red clover) contaminated with *Rhizoctonia leguminicola*.[27] This fungus produces a mycotoxin (slaframine), which has parasympathomimetic properties. The excess salivation disappears once the animal stops feeding on the plant.

Brainstem and Cerebral Disease

A neurological examination is necessary to assess the brain, brainstem, and spinal cord to determine whether the problem is focal, multifocal, or diffuse, and to determine whether the problem is peripheral or central. Lesions in the nucleus ambiguus and in the swallowing center of the medulla oblongata will result in dysphagia, but also affect adjacent structures resulting in depression, ataxia, weakness, and signs of other cranial nerve disease.[19] Diffuse brain disease can result in dysphagia without lesions in the medulla oblongata, as a result of interference with the voluntary, higher motor control of swallowing.[19] Equine viral meningitis, verminous encephalitis, moldy corn poisoning, tetanus, equine protozoal myelitis, and other diseases affecting the cerebrum and brainstem can result in dysphagia. Lead toxicity in horses is a combination of central and peripheral nerve dysfunction. Common signs of lead toxicity include laryngeal hemiplegia, dysphagia, muscle fasciculations, hyperesthesia, depression, and weight loss. Equine nigropallidal encephalomalacia is a progressive degenerative disease that primarily results in dysphagia and is due to chronic ingestion of Yellow Star Thistle (*Centaurea solstitialis*), Russian knapweed (*C. repens*), or Malta star thistle (*C. melitensis*).[28] These plants are more common in the western United States. The exact toxic agent is unconfirmed, but is believed to be DDMP (dihydro-dihydroxy-methyl-pyrane). Experimental feeding trials have shown that horses

must consume large amounts of the plant over a long period of time (weeks to months) before clinical signs occur.[28] Horses do not usually eat these plants, provided there is other suitable vegetation. However, once horses begin to eat these plants, they may selectively seek them out. The onset of clinical signs is sudden. The first clinical sign is a lack of coordination of the facial and oral muscles responsible for prehension and chewing.[28] Horses may still be able to swallow food and water if it is placed at the back of the throat. Horses may attempt to drink by submersing their muzzle deeply into water. The facial muscles become hypertonic and rigid. There may be constant, ineffective chewing movements. Some horses may only have difficulty with prehension, and others are unable to eat at all. Horses lose weight, become depressed, and will starve to death. Less severely affected horses may survive for a while by "scooping feed," but complete recovery has never been documented. Diagnosis is made by necropsy, with well-defined cavitated areas of liquefactive necrosis of the substantia nigra and the globus pallidus. Equine nigropallidal encephalomalacia is characterized by a highly selective pattern of lesions localized to brain regions rich in dopamine cell bodies and axons.[28,29] Antemortem diagnosis by magnetic resonance imaging is reported.[28,29]

Toxic causes of neurologic disease are further discussed in Section 3, Chapter 26.

Cranial Nerve Disease

Careful evaluation of the cranial nerves is important as many of these nerves (sensory and motor) are necessary for eating. Facial nerve paralysis is common in horses, and a sequela to several diseases such as trauma, otitis media, equine protozoal myelitis, and other CNS diseases. The majority of horses with unilateral facial nerve paralysis learn to adapt and do not have significant difficulties eating. Saliva may drool from the lips, because of the lack of muscle tone. Occasionally, a small amount of food may remain in the cheeks on the affected side. Bilateral facial nerve paralysis is reported to result in severe dysphagia in horses.[19] Diseases affecting the trigeminal nerve are much less common but could include trauma, equine protozoal myelitis, or infectious and toxic diseases of the CNS. Diseases of the mandibular branch of the trigeminal nerve can result in muscle atrophy of the masseter, temporalis, and distal belly of the digastricus muscles on the affected side.[19] Unilateral atrophy is not usually associated with major difficulties in chewing food. However, bilateral atrophy can result in difficulty in chewing, food falling out of the mouth, a dropped mandible, and the tongue protruding over the incisor teeth.[19] Tongue protrusion can also be seen in horses with head swelling due to jugular vein thrombosis or severe glossitis. Diagnosis is confirmed by observation and physical examination.

Diseases of the guttural pouches can result in dysphagia because several cranial nerves (including the glossopharyngeal, vagus, and hypoglossal nerves), the sympathetic trunk, and the cranial cervical ganglion lie beneath the lining of the medial compartment.[30] The glossopharyngeal, vagus, and hypoglossal nerves can be seen in the medial compartment of the guttural pouch.[30]

Diseases of the guttural pouch resulting in dysphagia include mycosis, trauma, iatrogenic administration of irritating substances, and empyema. Diagnosis of guttural pouch disease resulting in dysphagia is usually straight forward and best achieved by endoscopic examination.

The most common clinical signs associated with guttural pouch mycosis are nasal discharge (uni- or bilateral), dysphagia, and profuse epistaxis not induced by exercise. Other neurological disorders associated with guttural pouch mycosis include laryngeal hemiplegia, Horner's syndrome, and atrophy of the tongue.[31,32] Diagnosis of guttural pouch mycosis is achieved by upper airway endoscopy. Extra care (such as preparation of surgical facilities) is recommended when attempting to examine a bleeding guttural pouch, as removal or disruption of a blood clot could result in fatal hemorrhage. Vascular occlusion, by transarterial coil embolization, is the recommended treatment of choice for guttural pouch mycosis resulting in epistaxis.[31,32] Of 23 horses presented for epistaxis, 20 made complete recovery by transarterial coil embolization.[31] The success of either medical or surgical treatment for dysphagia due to mycotic infections is much poorer. In seven horses with epistaxis and dysphagia treated by surgical occlusion and topical antifungal therapy, there was complete resolution of dysphagia in two horses, mild dysphagia (but the ability to maintain body weight) in two horses, and three horses were euthanized due to the persistence of dysphagia.[33] Medical treatment in five horses with dysphagia only

resulted in euthanasia of three horses (due to the persistence of dysphagia).[33] Of the two surviving horses, one had complete resolution of the dysphagia and the second horse still had low-grade dysphagia at discharge.[33] Church *et al*. (1986)[34] reported that none of their five horses with dysphagia showed any improvement despite ligature of the internal carotid artery in one horse and lengthy medical treatment in the other four horses. The necessity of medical treatment is questioned by some clinicians.[31,32] A recent case series describes transarterial coil embolization (with no medical treatment) in 11 dysphagic horses with guttural pouch mycosis.[31] Resolution of the dysphagia in nine of the 11 horses occurred, and only two horses were euthanized due to the persistence of dysphagia.[31] It is difficult to predict the outcome in dysphagic horses due to guttural pouch mycosis, even when there is complete regression of the mycotic plaque. The presence of scar tissue around nerves many months after treatment might be an explanation for the persistence of dysphagia in the absence of mycotic lesions.[31–33]

Basilar skull fractures and severe hemorrhage secondary to rupture of the longus capitis or rectus capitis ventralis muscles are reported in horses that rear over backward and strike their head.[35] The most common clinical signs include loss of consciousness, ataxia, and facial and vestibular nerve dysfunction; however, dysphagia has been reported.[36] Empyema of the guttural pouch most commonly results in nasal discharge, cough, fever, retropharyngeal swelling, and inspiratory stridor.[37] However, dysphagia is also reported in 8% of horses with guttural pouch empyema.[37] Guttural pouch empyema is usually resolved by guttural pouch lavage, systemic antibiotics, and nonsteroidal antiinflammatory drugs. In some cases, topical administration of antibiotics into the guttural pouch is recommended. However, iatrogenic damage of the nerves lining the guttural pouch by lavage with irritating solutions can also result in dysphagia.

Esophageal Disease

Primary esophageal neurological diseases are very uncommon in horses. Megaesophagus is a chronic dilation of the esophagus and is most commonly secondary to a previous obstruction. Megaesophagus caused by primary esophageal dysfunction is rare, and there are a few case reports of decreased ganglial cells or neural elements in the esophageal wall. However, there is one report of 18 horses with megaesophagus and no history of obstruction.[38] Horses were young (0 days up to 2 years of age). Fourteen of these horses were Friesian horses, and the authors suggested that megaesophagus could be a recessive hereditary abnormality.[38] The prognosis for megaesophagus is extremely poor.

Neuromuscular Disease

Diseases affecting the neuromuscular junction resulting in dysphagia include botulism, tick paralysis, and grass sickness. The initial clinical signs of botulism include dysphagia, decreased tongue, eyelid, and ear tone.[25,39] Clinical signs progress to generalized muscle weakness, recumbency, and respiratory paralysis. Reduced tongue tone and slow tongue retraction are characteristics of botulism that usually occur before the onset of obvious muscle weakness.[26] Although dysphagia is commonly seen in most cases of botulism, dysphagia is not always apparent in horses with type C botulism.[26,39] Botulism is further discussed in Section 3, Chapter 17.

Tick paralysis is most commonly reported in dogs, but has also been reported in sheep, cattle, humans, and llamas. Tick paralysis in horses is not well documented, but is mentioned in a few equine texts. The author is aware of suspected tick paralysis in a group of miniature horse yearlings. Clinical signs in other species are similar to botulism, characterized by a flaccid paralysis, ptosis, and dysphagia.[40,41] Ticks within North America which have been incriminated in other species include *Dermacentor andersoni* (Rocky Mountain Wood tick) and *Dermacentor variablilis* (American dog tick).[40] Tick paralysis in Australia is due to *Ixodes holocyclus*.[40] In humans, tick paralysis can differ from botulism as the weakness begins in the limbs and progresses to muscles of the head (resulting in dysphagia).[41] The disease is inadequately described in the horse to determine whether this is also characteristic in horses. Diagnosis of tick paralysis is made by ruling out other diseases, and response to therapy. Removal of the tick in North America results in obvious improvement within 24 h, and complete recovery in 72 h. However, the weakness caused by the Australian tick may continue to progress even after tick removal.

Grass sickness is defined as a dysautonomia characterized by pathological lesions in the autonomic ganglia, enteric plexi, and specific nuclei in the

CNS.[42–46] Grass sickness is reported in the United Kingdom, Europe, and is also reported in several countries in South America. Clinical signs of grass sickness are characterized as acute, subacute, or chronic according to the duration and severity of clinical signs. The majority of horses with grass sickness are dysphagic and depressed. The dysphagia is caused by abnormalities of the cranial nerves and results in drooling of saliva, feed in the nostrils, impacted feed in the buccal pouches, and difficulties in esophageal transport. Other clinical signs of acute grass sickness include colic, increased heart rate, muscle tremors, bilateral ptosis, small intestinal distension, and mild secondary impaction of the large colon. Diagnosis of grass sickness is often based on clinical signs. However, conformation of grass sickness is achieved by observation of histopathological changes to enteric nerve plexi. Characteristic neural degenerative changes of the ganglia include chromatolysis, nuclear degenerative changes, cell death and neuronophagia, cytoplasmic vacuolation, and spheroid formation. Grass sickness is regarding as a fatal disease, resulting in ileus of the gastrointestinal tract, dysphagia, and weight loss, which most likely is associated with an unidentified neurotoxin. Grass sickness is consistently associated with grazing grass.[42] There is evidence that toxicoinfection with *Clostridium botulinum* type C may be involved with the pathogenesis of grass sickness.[43–46] Hunter *et al.* (2001)[45] demonstrated the presence of one of the toxins produced by *C. botulinum* type C in 44% of horses with grass sickness compared to 4% in control horses. Horses with grass sickness have significantly lower antibody concentrations to *C. botulinum* and its C type toxin than horses that either have contact with horses with grass sickness or have grazed frequently affected land.[45,46]

BLINDNESS, ANISOCORIA, AND STRABISMUS

Martin Furr

Blindness can be difficult to document in horses as they can accommodate to loss of vision to an amazing degree if they are confined to a small area. It is important to examine the horse in a strange environment, taking precautions to prevent accidental injury should the horse fall or startle.

Blindness can arise from disease of the eye itself, or the neural connections including the retina, optic nerve, optic tract, or visual cortex. Ocular disease is not discussed in this chapter, and the reader is referred to textbooks of equine ophthalmology for discussion of ocular disease. Neurogenic blindness rarely occurs alone, and additional neurologic abnormalities are often noted. This is also true for abnormalities of eye position, motion, and pupillary size, such as anisocoria, strabismus, or nystagmus. These conditions usually reflect midbrain disease, which can arise from any number of conditions, and they are not specifically addressed in this chapter.

Forebrain disease often results in blindness, associated with a depressed menace response. Disease of the visual cortex (central or cerebral amaurosis) results in deficient vision, with normal pupillary light responses (PLRs) and absent menace. If the cerebral disease is unilateral, the blindness will be expressed in the contralateral eye. Optic nerve and optic tract lesions will result in loss of the PLR in the ipsilateral and contralateral eye. The indirect PLR is intact in the ipsilateral eye. If the optic chiasma is affected, both the direct and indirect PLRs are deficient in both eyes. Determination of the portion of the visual pathways involved is helpful in determining the etiology, and in planning further diagnostic testing, treatment, and establishing a prognosis. The eye should be carefully examined to ensure that it is not the source of the blindness prior to considering neurogenic causes.

A number of conditions have been associated with neurogenic blindness in the horse. These include toxic, traumatic, and infectious causes. Head trauma is a common injury in the horse, and blindness can result even after recovery from other neurologic deficits, or from even apparently mild trauma that does not lead to unconsciousness.[47] Traumatic optic nerve atrophy presumably results from stretching and/or avulsion of the nerve following a deceleration injury. Typically, the ocular fundus is normal initially, but 3–4 weeks after the incident fundic examination finds a pale optic nerve with decreased retinal vessels.[47] Treatment of such cases appears unrewarding and blindness is permanent. Meningitis arising from bacterial, viral, parasitic, and mycotic organisms has been reported to be associated with blindness in the horse.[48–55] In such cases, blindness is only a part of the clinical presentation, and profound neurologic abnormalities are usually present indicating more widespread CNS disease.

Similarly, a variety of toxins may have blindness as a part of the clinical signs, but blindness is never the sole sign in such cases. Overdosage with ivermectin can result in transient blindness, and blindness is a major component of the clinical presentation of horses with fumonisin B intoxication ("moldy corn disease").[56,57] Horses with leukoencephalomalacia demonstrate diffuse signs of forebrain disease including dementia. The ingestion of *Sypandra* species, found in Western Australia, can result in blindness and ataxia. Iatrogenic causes include air embolism and intracarotid injection. Horses and foals will often demonstrate transient blindness following a seizure from any cause (Table 8.4).

The evaluation of horses in which blindness has been detected should include a careful history and physical examination, and a complete neurologic examination to ensure that no other neurologic deficits are present. A variety of clinicopathologic test, imaging techniques, and electrodiagnostic procedures exist to aid in the evaluation, and the tests selected will depend upon the history and physical examination findings.

A careful history to evaluate the duration and nature of onset of the illness is necessary. Specific questions should be asked about previous treatments, recent dental procedures, vaccinations, or other injections. These are important because owners may not associate these events with the blindness and may not report them without specific questioning. The author has seen blindness associated with meningitis following inappropriately performed dental treatments for example. Upper airway infections or sinusitis may precede bacterial meningitis which can cause blindness. Trauma and intoxications have an abrupt onset, while infectious disease may have a more insidious onset. Congenital disease will be seen in young animals, and night blindness has been reported in Appaloosa horses. This is expressed as poor vision in low light conditions, which may lead to stumbling or shying at objects at dusk, but not during bright light. In addition, horses affected with nyctalopia may show a dorsal or dorsomedial eye deviation.[58]

Nutritional history is also important, as prolonged feeding of a vitamin A-deficient diet (in an experimental setting) has resulted in blindness and ataxia. Naturally occurring cases of vitamin A deficiency in the horse have not been described and may not occur.

Table 8.4. Neurogenic Causes of Blindness in the Horse

Nyctalopia
Head trauma
Cholesterol granuloma
Anesthetic associated cerebral necrosis
Bacterial meningitis
Cerebral abscess
Caudal tentorial herniation
Viral meningitis
Cryptococcal meningitis
Parasitic encephalitis
Mycotic encephalitis (secondary to guttural pouch mycosis)
Equine protozoal myeloencephalitis
Thiamine deficiency
Hypoxic-ischemic encephalopathy
Pars intermedia adenoma
Hepatoencephalopathy
Toxicity
Sypandra spp.
Ivermectin overdose
Leukoencephalomalacia
Inadvertent intra-arterial injection
Air embolism

Masses and fractures may be revealed by radiography, and radiographs of the head are always indicated in horses in which trauma is suspected; however, interpretation can be difficult. Magnetic resonance imaging or CT scans may be superior, and nuclear scintigraphy may also be employed. Endoscopic evaluation of the upper airways and guttural pouches is indicated to identify guttural pouch disease, or masses that may involve the orbit.

Routine clinicopathologic assays are indicated as part of a minimum database, but most conditions causing blindness are unlikely to lead to specific clinicopathologic abnormalities. Bacterial infections, tumors, or abscesses will result in characteristic inflammatory changes in the complete blood cell count, but these are nonspecific. If the physical and neurologic examination suggest CNS disease, a CSF evaluation is indicated, which may be diagnostic. Finally, electrodiagnostic testing of function can be performed; however, this provides little etiologic information.

Table 8.5. Summary of Clinical Examination Findings that May Assist in the Evaluation of Vision in the Horse

		Menace Response		Pupillary Light Response	
Lesion Location	Vision	Ipsilateral Stimulation	Contralateral Stimulation	Ipsilateral Light	Contralateral Light
Unilateral retina optic nerve	Abnormal	Absent	Present	Absent	Normal
Unilateral optic tract and lateral geniculate nucleus	Abnormal	Present	Absent	Fixed	Normal
Unilateral visual cortex	Abnormal	Present	Absent	Normal	Normal
Unilateral oculomotor nerve or nucleus	Normal	Absent	Present	Mydriasis	Normal
Bilateral retina optic nerve or optic chiasma	Abnormal	Absent	Absent	No response	No response
Bilateral visual cortex	Abnormal	Absent	Absent	Normal	Normal

HORNER'S SYNDROME

Ptosis, miosis, enophthalmos, and protrusion of the nictitating membrane, associated with sweating of the face and cranial cervical region (to C2) constitute Horner's syndrome.[59] As the syndrome is usually unilateral, the sweating is characteristically noted to be well delineated and not cross the midline of the head. Dilation of facial vessels and hyperemia of nasal and conjunctival membranes are also seen in some cases. These signs arise due to interruption of the sympathetic innervation of the structures. The sympathetic tract arises from the spinal cord at T1–T3, pass through the cervicothoracic ganglia, and ascend in the vagosympathetic trunk. From this point, the nerve fibers enter the cranial cervical ganglia beneath C1 in the wall of the guttural pouch.[60] The close anatomic association between the vagosympathetic trunk and the jugular vein makes trauma associated with intravenous injections a common cause of Horner's syndrome, but damage to any portion of the nerve, from its origin to termination, can result in the characteristic clinical signs.

Conditions that have led to or have been associated with Horner's syndrome include perivascular injections and jugular trauma, guttural pouch mycosis, trauma to the basisphenoid region, cervical abscesses, periorbital masses, esophageal rupture, and cervical trauma.[59] The syndrome has also been seen following apparently uncomplicated jugular vein injection.[60] Spinal cord lesions affecting the tectotegmental tract in the cervical region may also give rise to Horner's syndrome.

Diagnosis is usually by direct observation, as the syndrome is quite characteristic. However, preganglionic and postganglionic lesions can be differentiated by application of 0.1 ml of 1:1000 epinephrine solution to the eye. In horses with a postganglionic lesion, mydriasis is noted within 20 min, while mydriasis is delayed (30–50 min) in horses with a preganglionic lesion.[59] Treatment and prognosis of Horner's syndrome depends upon proper diagnosis of the inciting cause.

REFERENCES

1. Johnson PJ, Constantinescu GM, Frappier BL. 2001. The vestibular system. Part I: anatomy, physiology and clinical signs from altered vestibular function. *Equine Vet Educ* 3:136–40.

2. Johnson PJ, Kellam LL. 2001. The vestibular system. Part II: differential diagnosis. *Equine Vet Educ* 3:185–94.
3. Raphel, C. 1982. Brain abscess in three horses. *J Am Vet Med Assoc* 180:874–7.
4. Mair T, Pearson G. 1990. Melanotic hamartoma of the hind brain in a riding horse. *J Comp Pathol* 102:239–43.
5. Teuscher E, Vrins A, Lemaire T. 1984. A vestibular syndrome associated with *Cryptococcus neoformans* in a horse. *Zent Vet Med* 31:132–9.
6. Blythe L, Watrous B, Schmitz J. 1984. Vestibular syndrome associated with temporohyoid joint fusion and temporal bone fracture in three horses. *J Am Vet Med Assoc* 185:775–81.
7. Walker AM, Sellon DC, Cornelisse CJ. 2002. Temporohyoid osteoarthropathy in 33 horses (1993–2000). *J Vet Int Med* 16:697–703.
8. Hassel DM, Schott HC, Tucker RL, *et al*. 1995. Endoscopy of the auditory tube diverticula in four horses with otitis media/interna. *J Am Vet Med Assoc* 207:1081–4.
9. Divers TJ, Ducharme NG, de Lahunta A, *et al*. 2006. Temporohyoid osteoarthropathy. *Clin Tech Equine Pract* 1:17–23.
10. Bentz BG, Bentz BG, Ross MW. 1997. Otitis media/interna in horses. *Compend Contin Educ Pract Vet* 19:524–33.
11. Blythe LL, Watrous BJ, Shires MH, *et al*. 1994. Prophylactic partial stylohyoidostectomy for horses with osteoarthropathy of the temporohyoid joint. *J Equine Vet Sci* 14:32–6.
12. Pease AP, Van Biervliet J, Dykes NL. 2004. Complication of partial stylohyoidectomy for treatment of temporohyoid osteoarthropathy and an alternative technique in three cases. *Equine Vet J* 36: 546–50.
13. Stick JA, Wilson T, Kunze D. 1980. Basilar skull fractures in three horses. *J Am Vet Med Assoc* 176:228–31.
14. Reed SM. 1993. Management of head trauma in horses. *Compend Contin Educ Pract Vet* 15:270–6.
15. Marshall A, Byars T, Whitlock R. 1981. Brainstem auditory evoked response in the diagnosis of inner ear injury in the horse. *J Am Vet Med Assoc* 178:282–6.
16. Rolf S, Reed S, Melnick W. 1987. Auditory brainstem response testing in anesthetized horses. *Am J Vet Res* 48:910–4.
17. Mayhew IG, Washbourne JR. 1997. Brainstem auditory evoked potentials in horses and ponies. *Vet J* 153:107–13.
18. MacKay, RJ. 2001. On the true definition of dysphagia. *Compend Contin Educ* 23:1024–7.
19. Mayhew IG. 1989. *Large Animal Neurology A Handbook for Veterinary Clinicians*. Philadelphia: Lea & Febiger.
20. Watrous BJ. 1992. Dysphagia and regurgitation. In *Veterinary Gastroenterology*, edited by Anderson NY, 137–57. Malvern: Lea & Febiger.
21. Klebe EA, Holcombe SJ, Rosenstein D, *et al*. 2005. The effect of bilateral glossopharyngeal nerve anaesthesia on swallowing in horses. *Equine Vet J* 37:65–9.
22. Holcombe SJ. 2000. Upper airway dysfunction and inflammation. *Proc 18th Annu Meet ACVIM* 602–3.
23. Tessier C, Holcombe SJ, Derksen FJ, *et al*. 2004. Effects of stylopharyngeus muscle dysfunction on the nasopharynx of the exercising horse. *Equine Vet J* 36:318–23.
24. Holcombe SJ, Derksen FJ, Stick JA, *et al*. 1998. Effect of bilateral blockade on the pharyngeal branch of the vagus nerve on soft palate function in horses. *Am J Vet Res* 59:504–8.
25. Ducharme NG, Hackett RP, Gleed RD, *et al*. 1999. Pulmonary capillary pressure in horses undergoing alteration of pleural pressure by imposition of various upper airway resistive loads. *Equine Vet J Suppl* 30:27–33.
26. Whitlock RH, Buckley C. 1997. Botulism. *Vet Clin North Am Equine Pract* 13:107–28.
27. Osweiler GD. 2001. Mycotoxins. *Vet Clin North Am Equine Pract* 17:547–66.
28. Barr CA, Reagor JC. 2001. Toxic plants. What the horse practitioner needs to know. *Vet Clin North Am Equine Pract* 17:529–46.
29. Sanders SG, Tucker RL, Bagley RS, *et al*. 2001. Magnetic resonance imaging features of equine nigropallidal encephalomalacia. *Vet Radiol Ultrasound* 42:291–96.
30. Holcombe SJ, Ducharme NG. 2004. Upper airway function of normal horses during exercise. In *Equine Sports Medicine and Surgery*, edited by Hinchcliff KW, Kaneps AJ, Geor RJ, 539–41. Philadelphia: Saunders.
31. Lepage OM, Piccot-Crezollet C. 2005. Transarterial coli embolisation in 31 horses (1999–2002) with guttural pouch mycosis: 2-year follow-up. *Equine Vet J* 37:430–4.
32. Lepage OM, Perron MF, Cadore JL. 2004. The mystery of fungal infections in the guttural pouches. *Vet J* 168:60–4.
33. Greet TR. 1987. Outcome of treatment in 35 cases of guttural pouch mycosis. *Equine Vet J* 19:483–7.
34. Church S, Wyn-Jones G, Parks AH, *et al*. 1986. Treatment of guttural pouch mycosis. *Equine Vet J* 18:362–5.

35. Sweeney CR, Freeman DE, Sweeney RW, *et al*. 1993. Hemorrhage into the guttural pouch (auditory tube diverticulum) associated with rupture of the longus capitis muscle in three horses. *J Am Vet Med Assoc* 202:1129–31.
36. Knight AP. 1977. Dysphagia resulting from unilateral rupture of the rectus capitus ventralis muscles in a horse. *J Am Vet Med Assoc* 170: 735–8.
37. Judy CE, Chaffin MK, Cohen ND. 1999. Empyema of the guttural pouch (auditory tube diverticulum) in horses: 91 cases (1977–1997). *J Am Vet Med Assoc* 215:1666–70.
38. Broekman LEM, Kuiper D. 2002. Megaesophagus in the horse. A short review of the literature and 18 own cases. *Vet Q* 24:199–202.
39. Kinde H, Bettey RL, Ardans A, *et al*. 1991. *Clostridium botulinum* type C intoxication associated with consumption of processed alfalfa hay cubes in horses. *Am J Vet Res* 199:742–6.
40. Malik R, Farrow BRH. 1991. Tick paralysis in North America and Australia. *Vet Clin North Am Small Anim Pract* 21:157–71.
41. Zhongzeng L, Turner RP. 2004. Pediatric tick paralysis: discussion of two cases and literature review. *Pediatric Neurol* 31:304–7.
42. Newton JR, Hedderson EJ, Adams VJ, *et al*. 2004. An epidemiological study of risk factors associated with the recurrence of equine grass sickness (dysautonomia) on previously affected premises. *Equine Vet J* 36:105–12.
43. Hedderson EJ, Newton JR. 2004. Prospects for vaccination against equine grass sickness. *Equine Vet J* 36:186–91.
44. McCarthy HE, French NP, Edwards GB, *et al*. 2004. Equine grass sickness is associated with low antibody levels to *Clostridium botulinum*: a matched case–control study. *Equine Vet J* 36:123–9.
45. Hunter LC, Poxton IR. 2001. Systemic antibodies to *Clostridium botulinum* type C: do they protect horses from grass sickness (dysautonomia)? *Equine Vet J* 33:547–53.
46. Hunter LC, Miller JK, Poxton IR. 1999. The association of *Clostridium botulinum* type C with equine grass sickness: a toxicoinfection. *Equine Vet J* 31:492–9.
47. Martin L, Kaswan R, Chapman W. 1986. Four cases of traumatic optic nerve blindness in the horse. *Equine Vet J* 18:133–7.
48. Hatfield CE, Rebhun WC, Dietz AE, *et al*. 1987. Endocarditis and optic neuritis in a quarter horse mare. *Compend Contin Educ Pract Vet* 9: 451–4.
49. Kornegay JN, Oliver JE, Gorgacz EJ. 1983. Clinicopathologic features of brain herniation in animals. *J Am Vet Med Assoc* 182:1111–6.
50. Raphel C. 1982. Brain abscess in three horses. *J Am Vet Med Assoc* 180:874–7.
51. Welsh RD, Stair EL. 1995. Cryptococcal meningitis in a horse. *J Equine Vet Sci* 15:80–2.
52. Lester GD. 1992. Parasitic encephalomyelitis in horses. *Compend Contin Educ Pract Vet* 14: 1624–30.
53. Hatziolos BC, Sass B, Albert TF, *et al*. 1975. Blindness in a horse probably caused by gutturomycosis. *Zent Vet Med* 22:362–71.
54. Wagner PC, Miller RA, Gallina AM, *et al*. 1978. Mycotic encephalitis associated with guttural pouch mycosis. *J Equine Med Surg* 2:355–9.
55. Dubey JP, Lindsay DS, Saville WJA, *et al*. 2001. A review of *Sarcocystis* neurona and equine protozoal myeloencephalitis (EPM). *Vet Parasitol* 95:89–131.
56. Hautekeete LA, Khan SA, Hales WS. 1998. Ivermectin toxicosis in a zebra. *Vet Hum Toxicol* 40:29–31.
57. McCue P. 1989. Equine leukoencephalomalacia. *Compend Contin Educ Pract Vet* 11:646–51.
58. Rebhun WC, Loew ER, Riis RC. 1984. Clinical manifestations of night blindness in the Appoloosa horse. *Compend Contin Educ Pract Vet* 6:S103–6.
59. Sweeney RW, Sweeney CR. 1984. Transient Horner's syndrome following routine intravenous injections in two horses. *J Am Vet Med Assoc* 185:802–3.
60. De Lahunta A. 1977. Lower motor neuron-general visceral efferent system. In *Veterinary Neuroanatomy and Clinical Neurology*, edited by deLahunta A, 110–124. Philadelphia: W.B. Saunders Co.
61. Jackson CA, deLahunta A, Dykes NL, *et al*. 1994. Neurological manifestation of cholesterinic granulomas in three horses. *Vet Rec* 135:228–30.
62. Cymbaluk NF, Fretz PB, Loew FM. 1978. Amprolium-induced thiamine deficiency in horses: clinical features. *Am J Vet Res* 39:255–61.
63. Firth EC. 1978. Horner's syndrome in the horse: experimental induction and a case report. *Equine Vet J* 10:9–13.
64. George LW. 1990. Diseases of the nervous system. In *Large Animal Internal Medicine*, edited by Smith BP, 901–1045. St Louis: C.V. Mosby Co.

9
Differential Diagnosis of Urinary Incontinence and Cauda Equina Syndrome

Martin Furr and Francesca Sampieri

CAUDA EQUINA SYNDROME

Martin Furr

The constellation of abnormal clinical signs referable to disease of the cauda equina is termed the cauda equine syndrome.[1,2] The cauda equina is defined as the spinal cord and nerve roots which lie caudal to the second sacral spinal cord segments. Due to the incongruity between the spinal cord segments and vertebral segments, the cauda equina is caudal to the lumbosacral junction. The clinical signs that comprise this syndrome include urinary and fecal incontinence, analgesia of the tail, perineal and perianal skin, rectum, and external genitalia.[1,2] Pelvic limb disease may also be present. Clients may report urine dribbling or urine scalding, sometimes associated with obvious tail paralysis. Rectal impactions leading to colic may be the initial complaint in some cases.[2] Penile protrusion in males may also be reported by owners. Muscle wasting of the rump and pelvic limbs can be seen, but this is uncommon.[1]

A careful physical and neurologic examination may find hypalgesia of the skin around the tail head and perianal and perineal regions. There may be a zone of hypersensitivity surrounding the area of reduced skin sensitivity.[2] The tail clamp reflex is often obviously weak, and the anal reflex is absent or weak. Inability to retract the penis, associated with loss of sensation of the penis and sheath, may be present in geldings. Lack of sensation of the udder is noted in mares. Rear limb ataxia and signs of muscle wasting of the pelvic limbs are uncommon but can be seen if spinal cord disease extends cranial to the cauda equina. Reproductive abnormalities (constant erections in males, flaccidity, and urine pooling in mares) may be seen.[1]

As noted above, the cauda equina syndrome is not a specific disease, simply a description of a similar group of clinical signs arising from damage to the cauda equina. Hence, a variety of different specific conditions may affect the cauda equine, giving rise to similar clinical signs. These can include developmental, inflammatory, toxic, infectious, or traumatic illnesses. Accurate diagnosis requires a careful physical and neurologic examination, and the use of various ancillary diagnostic techniques. Knowledge of the regional anatomy is helpful in delimitating the nature and extent of specific neurologic deficits that may be detected (Table 9.1).

As in any illness, obtaining a careful history of the problem is essential. Owners should be specifically questioned about the potential for trauma, as this is the most common cause. Falling over backward, breeding injuries, or lifting by the tail all can result in fractures with resultant clinical signs. Ascending infection may be seen in horses which have had a tail injury, have had their tails docked recently, or have had a tail block. As information regarding these circumstances may not be offered by the owner, specific questioning may be necessary. Information about in-contact animals should be obtained to support equine herpesvirus 1 encephalitis (EHV-1) infection, and vaccination status for rabies and other

Table 9.1. Anatomic Innervations of the Nerves of the Cauda Equina

Spinal cord segment	Nerve	Innervation
S1–S2	Sciatic and gluteal	Muscles of pelvic limbs
S2–S4	Pudendal	External genitalia
S2–S4	Caudal rectal	Rectum, anus, perianal, and perineal skin
S2–S4	Pelvic	Pelvic plexus, parasympathetic to bladder, urethra, distal small colon, rectum, anus
	Coccygeal	Skin and muscle of tail

encephalitides should be obtained. Access to sorghum or Sudan grass should be ascertained to rule out sorghum cystitis. A complete physical examination will determine the presence of fever or depression suggesting an infectious process. Rectal examination to determine the presence of rectal impactions and urinary bladder tone is important; the sacrum should be carefully palpated to determine whether there are any areas of discontinuity, pain, or soft-tissue swelling (suggesting fracture); and the aorta and iliac arteries should be palpated for a pulse.

A complete neurologic evaluation should be completed to localize the neurologic signs and determine whether a more widespread problem exists. Presence of cranial nerve signs, specifically wasting of the muscles of the head, would suggest cauda equina neuritis ("polyneuritis equi"), or other diffuse CNS disease (often infectious). From a consideration of the origin of the nerve tracts, it is clear that spinal cord disease at the level of S2–3 should result in rectal impactions and urinary incontinence (UI), tail weakness, and hypalgesia of perianal skin. Failure to demonstrate all of these signs would suggest involvement of a nerve root or peripheral nerve, rather than the spinal cord. The presence of all of these signs associated with caudal ataxia suggests spinal cord disease cranial to the limits of the cauda equina (Table 9.2).

Routine clinicopathologic tests, such as complete blood cell counts, blood biochemistry analyses, and urinalysis, should be performed. These tests may reveal signs of inflammation, infection, or cystitis. A cerebrospinal fluid (CSF) evaluation is indicated in all such cases. Fractures caudal to the second sacral vertebra may not lead to any changes within the CSF. Also, epidural abscesses, discospondylitis, or soft-tissue swelling from trauma and fractures are unlikely to result in changes in the CSF. Alternatively, trauma cranial to S2 will usually result in CSF with blood, with a minimally increased white blood cell (WBC) count. Bacterial infections will result in an elevated CSF WBC count, while the changes with viral infections are more variable. In EHV-1 myeloencephalitis, the CSF is typically xanthochromic, with an increased protein and minimally increased WBC count, while infection with eastern or western encephalitis may have a more blood-tinged and serum discolored fluid with a higher monocyte count. In cases of cauda equina neuritis, CSF protein and WBC count are typically mildly increased.

Table 9.2. Causes of Cauda Equina Syndrome

- Trauma[1]
  - Exuberant callus formation
  - Soft-tissue swelling
  - Hematoma
- Sorghum toxicity[3]
- Epidural abscess
- Osteomyelitis[4]
- Neoplasia
  - Melanoma[5,6]
  - Lymphosarcoma[1]
- Bacterial meningitis
- Cryptococcal meningitis[2]
- Verminous myelitis
- *Listeria monocytogenes* myelitis[2]
- Equine herpesvirus 1 encephalitis
- Rabies[2]
- Equine protozoal myeloencephalitis[7]
- Cauda equina neuritis[8]

Due to the common association of trauma with cauda equina syndrome, various imaging modalities are important in the diagnostic evaluation. Radiography is useful and can be accomplished on smaller horses; more powerful equipment is necessary for adult animals, and it may not be possible even then. Pelvic radiographs taken with the horse anesthetized can be useful and should be considered on a case-by-case basis. Nuclear scintigraphy is probably more sensitive for the detection of fractures and infection and has become widely available. Lumbar myelography can be performed, and this may delineate extradural compression from tumors, soft-tissue swelling, displaced fractures, or hematomas. Ultrasonagraphy can also be very useful to aid the examination of this area.

Treatment for cauda equina syndrome is supportive and empirical. UI must be treated by frequent drainage; rectal impactions may require manual removal at frequent intervals. Treatment with mineral oil and a low bulk diet will aid the management of such horses. Anti-inflammatory drugs, including steroids, have palliative value and should be used. If infections are suspected or confirmed, antimicrobials are necessary, but in the authors' opinion, they are rarely successful in cases of osteomyelitis or epidural abscessation of this region. Cases suffering from trauma do well with stall rest and time. Surgical treatment including laminectomies and drainage of abscesses has been described and performed with some success.[2] Specific treatment is determined by the specific etiologic condition giving rise to the clinical signs. These treatments are detailed in appropriate sections throughout the text, and the reader is referred to these for further discussion.

URINARY INCONTINENCE IN HORSES

Francesca Sampieri

UI in horses is an uncommon disorder as shown by a recent case review with 37 documented cases in 8 years[3] and by the rare publications of the last 30 years. When present, however, UI represents a challenge for the clinician in terms of both accurate diagnosis and therapeutic management. There are many causes implicated in this disorder including infectious diseases, toxicants, congenital abnormalities, and traumatic injuries. Therapeutic approaches are limited in many cases.[3,4] The following discussion will be limited to neurogenic causes of incontinence. Additional textbooks can be consulted for discussion of other (non-neurologic) causes of UI.

Innervation and Neurophysiology of the Lower Urinary Tract

Both the sympathetic and parasympathetic system, along with somatic branches of the central nervous system, are necessary to coordinate the functions of the lower urinary tract. Although many aspects of the visceral afferent pathway are still unexplained in horses, one can extrapolate from people and other species of veterinary interest.[4]

Somatic innervation is primarily to the striated muscle of the urethra via a branch of the pudendal nerve, which originates from the second, third, and fourth sacral segments. The sympathetic nerve supply arises from spinal segments L1–4, via the hypogastric nerve, with preganglionic fibers synapsing in the caudal mesenteric ganglia. Postganglionic fibers supply the bladder (primarily beta 2) and proximal urethra (primarily alpha 1).[5]

Parasympathetic fibers innervating the bladder leave the spinal cord at the level of the second, third, and fourth sacral vertebrae, forming the pelvic nerve. These same spinal cord segments innervate the external genitalia and urethra.

The micturition reflex is an autonomic spinal cord reflex inhibited or favored by the cerebral cortex or brainstem centers. Facilitatory and inhibitory centers are mainly within the pons (brainstem), although there are others located within the cerebral cortex.[6]

As the bladder progressively fills (filling phase), there is a progressive increase in the tone of the muscles which comprise the urethral sphincters. During filling, the detrusor muscle remains relaxed due to the influence of pelvic nerve afferents and sympathetic nerves innervating the detrusor muscle. This is due to a reflex arc comprised of bladder stretch and pressure receptors, afferent pelvic nerve, spinal cord interneurons, and sympathetic tone in hypogastric nerve efferents. Upper motor neuron (UMN) influences from higher centers can also mediate the tone of urethral sphincters. This reflex allows the bladder to accumulate large volumes of urine, with little increase in intravesicular pressure.

Once the detrusor can no longer stretch, the intravesicular pressure increases, and sensory impulses are transmitted via the pelvic nerve to the pons, cerebrum, and cerebellum, giving the sensation of fullness. There is stimulation of descending UMNs in the reticulospinal tract to the sacral parasympathetic nuclei. Pelvic nerve impulses

stimulate detrusor muscle contraction, while stimulation of the pudendal and hypogastric sympathetic nerves initiate synchronous relaxation of the external sphincters, resulting in voiding.

Examination of the micturation reflex reveals that neurogenic incontinence can take one of two general forms—arising from dysfunction of either UMN or lower motor neurons (LMN). UMN disease is characterized by increased urethral resistance, arising from disinhibition of urethral sphincters. This makes urinary catheterization difficult and is usually associated with broad, deep spinal cord lesions anterior to the pelvic ganglion. LMN disease results in a paralyzed and atonic bladder.

Clinical Evaluation of UI

UI can be primary or secondary to other conditions. Chronicity may be established, depending upon the cause and the extent of the damage to the nervous structures or the detrusor muscle. In many cases, a specific diagnosis in horses cannot be determined.[3,7–9] Several primary diseases of the nervous system, such as sorghum or Sudan grass intoxication or spinal cord compressions, can lead to secondary UI.[3,10,11] It is useful, therefore, to categorize the UI as neurogenic or non-neurogenic. Non-neurogenic diseases can include those which bypass the urethral sphincter mechanism or are myogenic or idiopathic. The discussion will be limited to neurogenic causes.

Schott and colleagues (2004) reported that 11 of 37 horses had UI arising from a documented neurological disorder.[3] Various specific disorders were noted including equine protozoal myeloencephalitis, spinal cord compression, cauda equina syndrome, and equine degenerative myelopathy. Equine herpesvirus type 1 myeloencephalopathy[12,13] is classically associated with UI, but Sudan grass and sorghum poisoning, neoplasia and cryptococcal leptomeningitis have also been reported.[14–16]

Atonic Bladder Caused by Destruction of Sensory Nerve Fibers, or LMN Disease

Diseases leading to the destruction of sensory nerve fibers will result in UI, since this condition prevents the transmission of stretch signals from the bladder to initiate a micturation reflex. Disease of the LMN (which innervate the detrusor muscle) will also result in muscle weakness and inability to empty the bladder. In either case, the bladder fills to capacity, and urine is continuously passed a few drops at a time, through the urethra. This is overflow incontinence. In people, a common cause is a crush in the sacral region of the spinal cord.[6] In horses, certain infectious diseases such as equine herpes virus type 1 myeloencephalopathy,[17] vertebral osteomyelitis, epidural empyema, and cauda equina neuritis have resulted in this clinical presentation[4] along with myeloencephalopathies deriving from fungi or plant toxins,[9] parasitic myelitis,[10] or epidural administration of alcohol.

Uninhibited Neurogenic Bladder Caused by Lack of Inhibitory Signals by the Brain ("UMN Bladder")

Damage or disease of the UMNs in the brain or spinal cord will result in a syndrome characterized by frequent uncontrolled and incomplete micturition. This condition derives from partial damage in either the spinal cord or the brainstem that interrupts inhibitory signals influencing the micturation reflex. A small volume of urine will initiate an incomplete micturation reflex. Over time, this allows accumulation of urine in the bladder leading to distention and atony. Overflow incontinence can then be observed. Usually, it presents with signs of turgid bladder and increased urethral sphincter tone. Uncontrolled squirts of urine may be seen, but this is rather uncommon in horses.[3]

Automatic Bladder

Automatic bladder describes the condition of uncontrolled reflex empyting of the bladder without the modulating influence of the spinal cord UMNs. This occurs subsequent to spinal cord damage cranial to the sacral region. This is poorly described in horses with spinal cord trauma, as the period of spinal shock in such cases appears to be much shorter than that in other species.

Diagnosis

The diagnostic evaluation for horses with UI can be difficult, and a confirmed diagnosis may be elusive. An accurate history regarding previous or possible musculoskeletal injury, changes in work, vaccination, and deworming are important. Reproductive history of mares is of particular importance. On physical examination, unless, again, one deals with an acute neurologic disease, often the only, non-specific,

sign detected is large area of dirty, matted hair, wetness, and skin scalding on the medial aspect of the hind quarters. The type of incontinence (i.e., overflow, atonic, etc.) should be determined, if possible. The clinician should strive to determine whether the incontinence is due to a neurologic or non-neurologic cause.

A rectal palpation of the pelvic cavity is imperative, examining the bladder with care for tone, degree of filling, pain, and extension of the limits of the bladder in relation to the pelvic brim. In cases of cyanide poisoning (sorghum or Sudan grass), hard concretions can be palpated which are adhered to the bladder wall.[16,18] A trans-rectal ultrasonographic examination can be utilized to evaluate the bladder's content (sediment and fluid clarity), bladder wall, and pelvic soft tissues. Urethral catheterization should be performed next, immediately preceding urethral and bladder endoscopy. A musculoskeletal and lameness evaluation, with a careful neurologic examination, is important and should be completed as a part of the evaluation.

Standard clinicopathologic analyses (complete blood cell count, profile, and fibrinogen concentration) are often normal, but may be valuable in some cases and should be performed. Additional tests, such as serology, vitamin E assays, CSF analysis, or culture, will be determined by the clinical examination and history.

Radiographic investigation of the pelvis and the caudal spine are challenging but potentially very useful in the diagnosis of paravertebral abscesses or trauma. Nuclear scintigraphy may be more sensitive.

A variety of techniques have been utilized in both human and veterinary medicine to evaluate the dynamics of micturition in both normal and incontinent animals. These include cystometrography, urethral pressure profilometry (UPP), and simultaneous cystometry and uroflowmetry.[19] Cystometrography consists of pressure and volume recordings performed with the aid of fluid or gas in the bladder, during filling.[14] Bladder and urethral pressures profiles are pressure recordings obtained from the bladder and urethra using a cuffed catheter connected to a pressure transducer, and measurements are recorded as the catheter is withdrawn from the bladder, through the urethra. Urinary pressure profiling has been reported in a few horses, but its value in the diagnostic evaluation of equine neurologic disease is not established.[14,19]

Treatment

Goals of therapy for horses with UI are (1) to manage the incontinence itself, and (2) to provide treatment for the specific disease causing the incontinence. The following will discuss the management of incontinence; specific treatments of inciting neurologic conditions are discussed elsewhere in the text.

There are few drugs available to treat UI in horses, and these have been extrapolated from therapeutic protocols employed in small animals. The most commonly used and relatively successful drug is bethanechol hydrochloride (a cholinergic stimulant), which is usually used in cases due to bladder atony.[20,21] The primary effects of bethanechol on the lower urinary tract include increased detrusor muscle tone and intravesicular pressure and decreased bladder capacity.[22] It should not be used in cases of urinary outflow obstruction, due to the potential for bladder rupture.

The recommended dosage in horses for treatment for detrusor muscle atony ranges from 0.025 to 0.075 mg/kg BW SC q 8 h[20]; however preparations for subcutaneous administration are no longer commercially available. Pharmacies may be able to compound the drug, however. Doses ranging from 0.2 to 0.4 mg/kg PO q 8 or 6 h are suggested in dogs and have been employed in horses. The drug should not be given intramuscularly or intravenously. Overdosing causes excessive cholinergic stimulation, with the potential for clinical signs such as arrhythmias and colic.

If urinary outflow resistance is increased due to increased urethral tone, bethanechol can be given with diazepam or dantrolene for relaxation of the striated muscle fibers. Alternatively, phenoxybenzamine can be administered to achieve relaxation of the urethral sphincter.[23] Phenoxybenzamine is prohibitively expensive in the horse, and the utility of these drug combinations have not been determined in the horse.

The administration of α-antagonists (prazosin and phenoxybenzamine) has been recommended in those cases where an external urethral sphincter dysfunction is suspected, in order to reduce urethral resistance by blocking the α-mediated contraction of smooth muscle, in both the bladder neck and the urethra.

A starting dose of 5 mg prazosin PO q 8 h for an adult horse has been used successfully in two cases. Individual titration to effect is required, due to

interindividual variability, and the total dose should not exceed 10 mg, due to the potential for hypotension.

Keys for successful treatment of horses with UI are careful management of bladder distention and urine scalding.[3,9] It is also necessary that the primary neurologic disorder be successfully treated as well.

Bladder catheterization several times per day is recommended to prevent bladder distention and the potential for rupture. Maintaining a small residual volume is also expected to enhance healing of the detrusor muscle and optimize the chances for recovery of the micturation reflex. Repeated catheterization may become difficult due to urethral trauma, but this can be avoided by the use of an indwelling urethral catheter. Along with draining urine, lavage of the bladder to remove sabulous material may enhance the outcome.[4,9]

Finally, careful attention to care of urine scalding is important.[3,24] Constant cleaning and application of soothing protective ointment (e.g., vaseline) is recommended to prevent skin excoriations.

Prognosis

The prognosis for horses affected by UI is variable and may be unpredictable in individual cases. If the primary cause of the UI can be corrected surgically, as in case of congenital anomalies, the prognosis is good.[25–27] If UI manifests during acute neurological disease which resolves, it is likely that the incontinence will also resolve provided appropriate care is taken to ensure that prolonged bladder distention does not occur.

In contrast, the long-term prognosis is usually poor for chronically established UI, due to either detrusor dysfunction or a large atonic bladder.[3,4] Contributing factors may be that the underlying detrusor dysfunction was present before the problem became clinically recognizable and second, once sabulous urolithiasis becomes marked, the chances for a long-term recovery decrease considerably. In cases of Sudan grass or sorghum toxicity, if the ataxia, bladder atony, and cystitis are advanced and chronic, the chances of even partial recovery are small.[28]

To conclude, almost 68% of the horses were discharged from the hospital, but only 50% of the cases examined survived long term, counting a complete recovery only in 10 cases, of which the neurologic/idiopathic constituted unfortunately the minor part.[3] One should note that limitations to long-term survival are due to the requirement for constant nursing care, which often requires the intervention of skillful personnel or the training of very committed owners.

REFERENCES

1. MacKay RJ. 1997. Cauda equina syndrome. In *Current Therapy in Equine Medicine*, edited by Robinson NE, 311–4. Philadelphia: W.B. Saunders Co.
2. Pirie RS. 2003. Bladder, rectal, anal, and tail paralysis; perineal hypalgesia; and other signs of cauda equina syndrome. In *Current Therapy in Equine Medicine*, edited by Robinson NE, 755–60. Philadelphia: Saunders.
3. Schott HC, Carr EA, Patterson JS, *et al*. 2004. Urinary incontinence in 37 horses. *Proc Annu Meeting Am Assoc Equine Pract* 50:345–7.
4. Holt PE. 1997. Urinary incontinence in horses. *Equine Vet J* 9:81–4.
5. Bayly WM. 1998. Urinary incontinence and bladder dysfunction. In *Equine Internal Medicine*, edited by Reed SM, Bayly WM, 907–11. Philadelphia: W.B. Saunders Co.
6. Saper CB. 2002. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu Rev Neurosci* 25:433.
7. Attenburrow DP, James ED. 1981. Urinary incontinence in a pony mare. *Equine Vet J* 13:206–8.
8. Watson ED, McGorum BC, Keeling N, *et al*. 1997. Oestrogen responsive urinary incontinence in two mares. *Equine Vet Ed* 9:81–4.
9. Holt PE, Mair TS. 1990. Ten cases of bladder paralysis associated with sabulous urolithiasis in horses. *Vet Rec* 127:108–10.
10. Mayhew IG. 1999. The diseased spinal cord. *Proc Annu Meeting Am Assoc Equine Pract* 45:67–84.
11. Johnson PJ, Goetz TE, Baker GJ, *et al*. 1987. Treatment of two mares with obstructive (vaginal) urinary outflow incontinence. *J Am Vet Med Assoc* 191:973–5.
12. Friday PA, Scarratt WK, Elvinger F, *et al*. 2000. Ataxia and paresis with equine herpesvirus type 1 infection in a herd of riding school horses. *J Vet Intern Med* 14:197–201.
13. Reed SM, Toribio RE. 2004. Equine herpesvirus 1 and 4. *Vet Clin North Am Equine Pract* 20:631–42.
14. Kay AD, Lavoie JP. 1987. Urethral pressure profilometry in mares. *J Am Vet Med Assoc* 191:212–6.
15. Chaffin MK, Honnas CM, Crabill MR, *et al*. 1995. Cauda equina syndrome, discospondylitis, and a

paravertebral abscess caused by *Rhodococcus equi* in a foal. *J Am Vet Med Assoc* 206:215–9.
16. Adams LG, Dollahite JW, Romane WM, *et al*. 1969. Cystitis and ataxia associated with sorghum ingestion by horses. *J Am Vet Med Assoc* 155:518–24.
17. Wilson WD. 1997. Equine herpesvirus 1 myeloencephalopathy. *Vet Clin North Am Equine Pract* 13:53–72.
18. Van Kampen KR. 1970. Sudan grass and sorghum poisoning of horses: a possible lathyrogenic disease. *J Am Vet Med Assoc* 156:629–30.
19. Ronen N. 1994. Measurements of urethral pressure profiles in the male horse. *Equine Vet J* 26:55–8.
20. Jose-Cunilleras E, Hinchcliff KW. 1999. Renal pharmacology. *Vet Clin North Am Eq Prac* 15:647–64.
21. Lane IF, Fischer JR, Miller E, *et al*. 2000. Functional urethral obstruction in 3 dogs: clinical and urethral pressure profile findings. *J Vet Intern Med* 14:43–9.
22. Khanna OP, Heber D, Gonick P. 1975. Cholinergic and adrenergic neuroreceptors in urinary tract of female dogs. Evaluation of function with pharmacodynamics. *Urology* 5:616–23.
23. Khanna OP, Gonick P. 1975. Effects of phenoxybenzamine hydrochloride on canine lower urinary tract: clinical implications. *Urology* 6:323–30.
24. Laverty S, Pascoe JR, Ling GV, *et al*. 1992. Urolithiasis in 68 horses. *Vet Surg* 21:56–62.
25. Odenkirchen S, Huskamp B, Scheidemann W. 1994. Two congenital anomalies of the urinary tract in warmblood horses: ectopia ureteris and diverticulum vesicae. *Tierarztl Prax* 22:462–5.
26. Sullins KE, McIlwraith CW, Yovich JV, *et al*. 1988. Ectopic ureter managed by unilateral nephrectomy in two female horses. *Equine Vet J* 20:463–6.
27. Squire KR, Adams SB. 1992. Bilateral ureterocystostomy in a 450-kg horse with ectopic ureters. *J Am Vet Med Assoc* 201:1213–5.
28. Knight PR. 1968. Equine cystitis and ataxia associated with grazing of pastures dominated by sorghum species. *Aust Vet J* 44:257.

10
Electrodiagnostic Evaluation of the Nervous System

Veronique Lacombe and Frank Andrews

Evaluation of the nervous system in horses requires a comprehensive approach that includes signalment, history, and complete physical and neurologic examinations. The overall goal of a comprehensive approach is to confirm the presence or absence of neurologic disease and to localize the lesion to a focal or multifocal area of the nervous system. Once the horse has been examined, electrodiagnostic aids can be used to further refine and localize lesions within the nervous system and to differentiate neurologic from musculoskeletal disease.

Neurologic disease is characterized by altered cell electrical activity, and these changes can only be measured by sophisticated electronic equipment. The branch of medical science that measures this electrical activity is referred to as electrodiagnostics. Electromyography (EMG), auditory brainstem-evoked response (ABR) testing, and electroencephalography (EEG) are electrodiagnostic aids that help localize, diagnose, and aid in the prognosis of neurologic diseases. Electromyography (needle EMG) and nerve conduction studies (NCS) are used to evaluate lesions of the lower motor neuron or motor unit. In addition, the use of magnetic motor-evoked potentials can be coupled with an EMG to asses the functional integrity of motor pathways in the spinal cord.[1] ABR testing is used to identify the presence of diseases affecting the vestibulocochlear nerve (CN VIII) and its pathways within the brainstem. EEG is used to identify focal and diffuse cerebral lesions. These diagnostic aids, separately or collectively, should always be used in conjunction with a complete neurologic examination and can provide valuable information about the function of the neurologic system. These techniques are relatively noninvasive and, in many cases, can be done with mild sedation in the standing horse. Even when these techniques do not provide the information necessary to arrive at a diagnosis, they provide a more complete understanding of the disease process and with serial examinations can help determine prognosis.

ELECTROMYOGRAPHY

Needle EMG is the graphical recording of muscle cell electrical activity during contraction or at rest from a recording electrode placed in the muscle and does not involve muscle or nerve stimulation. The electrical activity of the muscle is amplified and converted into a digital and audio signal for capture by a computer. NCS, on the other hand, involve stimulating large myelinated peripheral nerves with electrical current and recording the resultant physiologic electrical activity from other segments of the nerve or from the muscles innervated by that nerve. Together, EMG and NCS aid in the localization, diagnosis, and prognosis of diseases of the motor unit, which consists of the ventral motor horn cell body (located in the ventral horn of the spinal cord), its axon (ventral root), peripheral nerve, myoneural junction, and the muscle fibers it innervates (Figure 10.1).

Instrumentation

Commercially available electromyographs are appropriate for examination of horses. The essential components of the electromyographs used in equine neurology are needle electrodes for recording electrical activity arising from muscles, a preamplifier and built-in amplifier to amplify the small voltage signal in the muscle fibers, and a computer monitor with attached speakers for viewing and hearing the

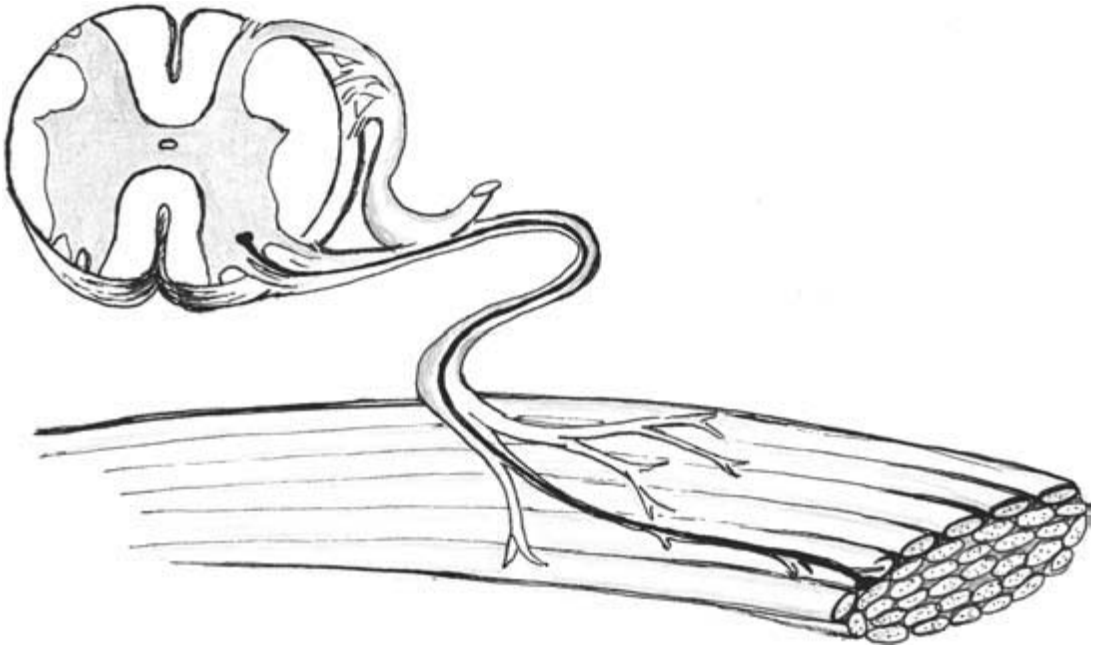


Figure 10.1. Illustration of the lower motor unit including the ventral horn cell in the spinal cord, ventral root, peripheral nerve, neuromuscular junction, and muscle.

high-frequency (10–10,000 Hz) muscle electrical potentials. Auditory output is essential since electromyographic potentials have characteristic sounds which help to confirm the visual signal. Optional equipment on most newer models include image and auditory capture systems for storage on a hard drive or portable media (CDs or memory sticks).

Standard disposable monopolar and concentric needle electrodes, ranging from 25 to 100 mm in length with diameters of 0.45 mm to 0.8 mm, are commonly used for electromyographic examination in horses. These electrodes provide a sampling area of approximately 0.068 mm,[2] which corresponds to approximately 30–50 muscle fibers. Self-adhesive surface Ag/AgCl electrodes have been used in horses but may be restricted to recording electrical activity from superficial muscles.[2]

Concentric electrodes consist of an outer 24-gauge needle (reference) with a central wire serving as a ground electrode. The concentric electrode is inserted in the subcutaneous tissue over or near a bony prominence (wing of atlas, spine of scapula, tuber coxae, and tuber ischii). A monopolar electrode, the preferred exploring electrode, is inserted into the muscle of interest, and recordings of muscle electrical activity are taken. Monopolar electrodes are coated with Teflon, except for the tip, to minimize electrical interference and limit the explored area to 30–50 motor units. Electromyographic examination can also be done using three monopolar electrodes: the ground electrode (25 mm), which is placed in the subcutaneous tissue over a bony prominence; a reference electrode (25–37 mm) placed in the subcutaneous tissue between the ground electrode and muscle to be explored; and finally the exploring electrode (37–75 mm) which is placed in the muscle of interest. Approximately 50 muscle fibers, an area with a 0.5-mm radius around the needle electrode, contribute to the observed electrical potential.[3] The needle electrodes should be kept in close proximity to reduce electrical interference. Different electrodes, the distance between electrodes, and types of patient ground will affect the size and duration of recorded electropotentials.[4]

Nerve Conduction Studies

The evaluation of nerve conduction velocities requires knowledge of topographic anatomy of

nerves and muscles. Instrumentation requires a stimulator capable of delivering up to a 150 V shock at durations of 0.1–3 ms. However, typically supramaximal stimulus can be obtained at 70–90 V for 0.1 s. Most standard electromyographs have built-in stimulators with adequate parameters to do NCS. The peripheral nerve to be assessed is located either by palpation or by using anatomic landmarks and then stimulated. The resultant muscle contraction can be palpated and observed, and the evoked muscle action potential, which has a thumping sound, can be viewed on the computer monitor. Once the nerve is stimulated at two different sites along the nerve, the latency is calculated, which corresponds to the nerve conduction velocity.

Electromyographic Examination

A history, physical, and neurological examination should always precede the electromyographic examination. This aids in localization of the lesion, shortens examination time, and minimizes trauma to the horse. Initially, horses are examined under mild sedation while restrained in stocks. Tranquilization with xylazine (0.2–0.6 mg/kg, intravenously), xylazine–butorphanol (0.2–0.6 mg/kg and 0.01–0.02 mg/kg, intravenously, respectively), or detomidine (0.01–0.02 mg/kg, intravenously) can be used. Examination of the animal prior to sedation aids in evaluating individual motor unit action potentials (MUAPs), summated MUAPs, and interference pattern. Normal and abnormal MUAPs can be evaluated with respect to amplitude and duration. Many MUAPs or an interference pattern can sometimes obscure low-amplitude abnormal potentials on the monitor and may require further examination under general anesthesia. The exploring electrode should be thrust briskly into the muscle and held until the animal completely relaxes. To assist relaxation, the animal can be forced to bear weight on the opposite limb. Once relaxation has occurred, the resting activity or any postinsertional activity of the muscle can be evaluated. At least four areas and depths of smaller skeletal muscles and six to eight areas and depths of large skeletal muscles should be evaluated when possible.[5]

A neurologic examination should be done on each case to localize the lesion so that the electromyographic examination can be performed in a systematic fashion to save time and limit pain to the patient. In cases of generalized muscle weakness or a suspected neuropathy, a comprehensive needle EMG examination should be done that includes the major extrinsic muscles of the pelvic limb, including the long digital extensor, gastrocnemius, deep digital flexor, semimembranosis, vastus lateralis, biceps femoris, and middle and superficial gluteal muscles; the epaxial or paravertebral muscles, segmentally from the sixth lumbar to the first cervical vertebrae; and finally, the extrinsic muscles of the forelimb, including the subclavius, infraspinatus, supraspinatus, deltoideus, biceps brachii, triceps brachii, extensor carpi radialis, superficial digital flexor, and deep digital flexor muscles. Other muscles may be included such as facial, laryngeal, esophageal, pectoral, coccygeal, and external anal sphincter if indicated by the neurologic examination. NCS and/or muscle biopsies can be done to further isolate and characterize suspected lesions or confirm a diagnosis (Table 10.1).

Nerve Conduction Studies

NCS are difficult to perform in the horse; consequently, they are not done routinely. The technique for assessing radial and median nerve conduction velocities in the horse has been reported.[6,7] Nerve conduction testing is used to evaluate the speed of conduction of large myelinated motor nerves. Nerve stimulation is very painful, and thus NCS are performed with the horse under general anesthesia and positioned in lateral recumbency with the affected side up.[5] The appropriate motor nerve is stimulated by monopolar needle electrodes inserted at or near the nerve, and an evoked MUAP from an innervated muscle is recorded by pick-up electrodes placed in a muscle innervated by this nerve. Contraction of appropriate muscles can be visualized or palpated and needle electrodes repositioned until a repeatable response is obtained. The normal limb can be used as a control. In the horse, radial nerve recordings can be taken from the extensor carpi radialis and abductor digiti longus (extensor carpi obliquus) muscles.[6,7] Median nerve recordings can be obtained from the humeral and radial heads of the deep digital flexor muscle.[6,7] Facial nerve conduction velocities can be taken from the levator nasolabialis by stimulating the buccal branch of the facial nerve just ventral to the facial crest.[5] Usually, a supramaximal stimulus is obtained at 70–90 V for 0.1 ms duration. NCS can be used to evaluate injuries to the radial, median, suprascapular, and facial nerves.

Table 10.1. Muscles, Nerves, and Nerve Roots Evaluated During a Routine Electromyographic Examination

Muscles	Peripheral Nerve	Spinal Nerve Root
Rear limb		
Long digital extensor	Peroneal nerve	L6 to S1
Gastrocnemius	Tibial nerve	S1 to S2
Deep digital flexor	Tibial nerve	S1 to S2
Semimembranosus	Ischiatic nerve	L5 to S2
Vastus lateralis	Femoral nerve	L4 to L6
Biceps femoris	Caudal gluteal, Ischiatic, and Peroneal nerves	L6 to S2
Middle gluteal	Cranial and caudal gluteal nerves	L5 to S2
Paravertebral		
Paravertebral muscles (segmentally)	Dorsal branches of ventral spinal	L6 to C1
Forelimb		
Subclavian	Pectoral nerve	C6, C7 (TI)
Supraspinatus and infraspinatus	Suprascapular nerve	C6, C7, C8
Delioideus	Axillary nerve	C6, C7, C8
Biceps brachii	Musculocutaneous nerve	C6, C7, C8
Triceps brachii	Radial nerve	C7, CS, TI
Extensor carpi radialis	Radial nerve	C7, C8, TI
Superficial digital flexor	Ulnar nerve	C8, TI, T2
Deep digital flexor	Ulnar and median nerves	C7, C8, T1, T2

Normal Electromyographic Potentials

Muscles can be examined at rest, under submaximal contraction and maximal contraction in the awake horse. However, muscle contraction is absent in the anesthetized horse so only resting activity can be examined. Furthermore, NCS can only be done in the horse under general anesthesia.

Insertional Activity

Insertional activity is short bursts of positive (downward) or negative (upward) high-amplitude, moderate- to high-frequency (<200 Hz) electrical spikes following insertion or movement of the exploring needle electrode in the muscle. In normal skeletal muscle, this activity lasts up to 300 ms after cessation of needle movement.[8] Insertional activity is likely caused by damage, mechanical irritation of muscle cells, or depolarization of muscle fibers directly adjacent to the EMG needle. Insertional activity response depends on the magnitude and speed of needle movement and is considered semiquantitative.[8] Positive sharp waves and fibrillation potentials may occur during or associated with needle insertion, but in normal muscle, should stop after cessation of needle movement. Damage of muscle fibers due to insertion of the needle is probably the source of these abnormal spikes. However, persistent positive sharp waves (more than two) and fibrillation potentials after needle insertion are considered abnormal and may suggest early muscle denervation.[8] Insertional activity has been reported to vary from 120 ms to 2 s in horses.[9,10] Mean (SD) insertional activity in the subclavius muscle of warmblood horses was 472 (103) ms or 561 (200) ms, which was significantly different than insertional activity in the triceps and vastus lateralis muscles, which was 519 (133) ms and 497 (114) ms.[11] The authors also found that the mean duration of insertional activity was significantly shorter in younger horses (13–18 months of age) when compared to older horses (18–21 years of age).[11] The clinical significance of this difference was not

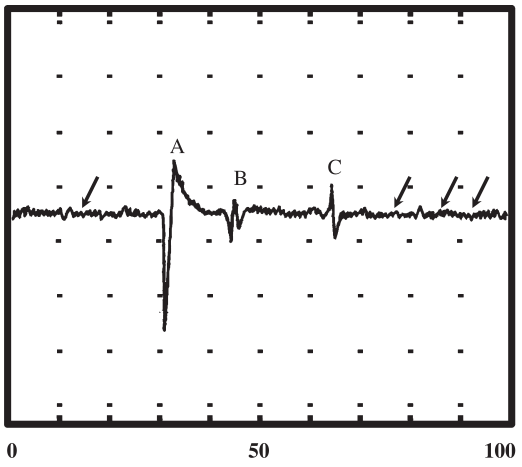


Figure 10.2. Electromyograph from the right middle gluteal muscle of a horse showing resting activity (postinsertional baseline, arrows), positive sharp wave (A), fibrillation potential (B), and a small motor unit action potential (MUAP) (C) with early denervation atrophy due to Equine Protozoal Myeloencephalitis.

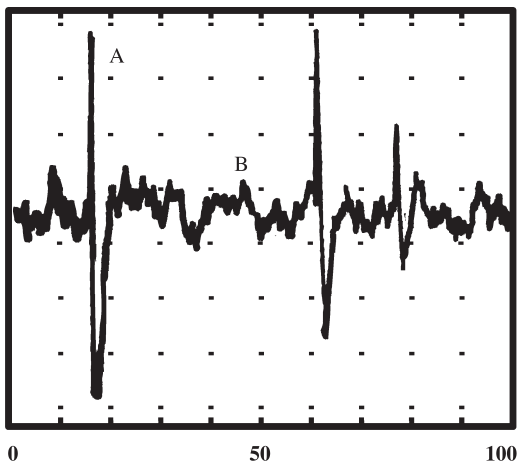


Figure 10.3. Electromyograph from the semitendinosus muscle showing end-plate spikes (A) and end-plate noise (B).

apparent, and because the range was similar to those published in other horses, these values appear to be suitable for use as normals in horses.

Resting and Spontaneous Activity

Resting activity (postinsertional baseline) is observed in relaxed muscle and is characterized by electrical silence and produces a flat baseline (see Figure 10.2). When the needle comes to rest near a nerve twig or end plate, the needle irritates small intramuscular nerve terminals, which results in the production of spontaneous activity which are referred to as spontaneous miniature end-plate potentials (MEPPs) and end-plate spikes. MEPPs in horses are approximately 25–100 μV in amplitude and 5–10 ms in duration and produce a low-pitched continuous noise.[11] These potentials are caused by the spontaneous release of acetylcholine from nerve terminal in the area near the needle electrode (see Figure 10.3). End-plate spikes, on the other hand, are high-amplitude (100–200 μV), short-duration (3–4 ms) intermittent spikes that make a popping sound.[12] End-plate spikes are thought to be single muscle fiber contractions secondary to needle electrode irritation of the nerve terminals. In human, these potentials are associated with dull pain, and repositioning the needle often eliminates their activity.

Motor Unit Action Potentials

MUAPs are voluntary or reflex muscle contractions that occur after insertion of the needle electrode. They represent the sum of a number of single muscle fibers potentials belonging to the same motor unit. MUAPs are described based on duration, amplitude, phases, turns, and recruitment pattern.[11] The MUAP duration is defined as the time from initial deflection to the final return to baseline. Amplitude is defined as the peak to peak measurement (see Figure 10.2). A phase is defined as the unit between departure from and return to baseline and can be counted as the number of baseline crossings plus one (see Figure 10.2). Number of turns is defined as a change in the direction of the signal independent of crossing the baseline (see Figure 10.2). Generally, normal MUAPs are potentials that are mono-, bi-, and triphasic, 3-10 ms in duration, and have an amplitude of approximately 1500 μV (range 500–3000 μV).[5] Normal values for various muscle in the horse have been previously reported and differ between muscles explored.[11] A few polyphasic potentials (more than four phases) can be seen in normal skeletal muscle but should not

exceed 5–15% of the total MUAPs observed during the examination.[5] In one study, the prevalence of polyphasic MUAPs in the subclavian muscle of horses was 7.7%.[11] The MUAPs can be observed when the horse is forced to bear weight on or retract a limb, resulting in contraction of that explored muscle. In lightly stimulated muscle, a single MUAP can be seen as a single motor unit is recruited (see Figure 10.2). As the muscle contraction becomes more intense, more motor units are recruited (see Figure 10.4), and the greater frequency of MUAPs appears on the computer monitor until the screen is filled, which results in an interference pattern (see Figure 10.5).[5,13,14] An interference pattern can obscure low-amplitude fibrillation or positive sharp wave potentials or polyphasic MUAPs; thus general anesthesia may be necessary.[15] Clinically, the number of phases and the duration of MUAPs are of greater importance than amplitude, because amplitude is influenced by muscles, age, and electrode position.[16]

Abnormal Electromyographic Potentials

Spontaneous activity in a relaxed muscle after cessation of needle movement may be clinically significant. Diseases affecting the lower motor unit (or final common path) can lead to altered muscle electrical activity, such as prolonged or decreased insertional activity, postinsertional activity, altered waveforms, and complex repetitive discharges (CRDs). Some abnormal electromyographic potentials are described in the following sections.

Prolonged or Decreased Insertional Activity

Prolonged electrical activity continuing 1 to 10 ms after insertion of the needle and its placement in the muscle is considered abnormal and is probably due to hyperirritability and instability of muscle fiber membrane.[16] This activity is most prominent 4–5 days after denervation in dogs.[17] Increased or prolonged insertional activity usually precedes the onset of other denervation potentials (fibrillation potentials and positive sharp waves) and may suggest early denervation atrophy,[16] but can also be seen in myotonic disorders and myositis.[18] Decreased insertional activity (decreased amplitude, duration, or both) may be associated with a decreased number of functioning muscle fibers and may suggest a long-standing neuropathy and/or myopathy. Infiltration within the muscle by connective tissue and fat can lead to a decreased number of muscle fibers, which in turn decreases insertional activity. Complete muscle fibrosis may result in loss of all insertional activity. Insertional activity may

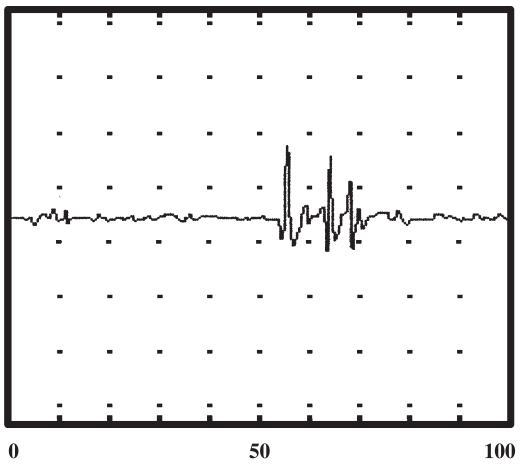


Figure 10.4. Electromyograph from the supraspinatus muscle showing 3 recruited motor unit action potentials (MUAPs).

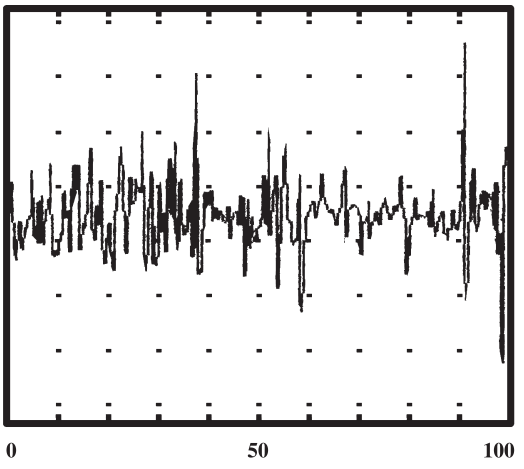


Figure 10.5. Electromyograph from the supraspinatus muscle showing an interference pattern due to strong recruitment of MUAPs due to muscle contraction from weight bearing.

also be absent when muscle fibers are functionally inexcitable, as occurs during attacks of familial periodic paralysis, when a faulty needle electrode is used, or when the needle is introduced into normal resting muscle.[8]

Polyphasic or Myopathic MUAPs

Myopathic MUAPs have a frequency of greater than four phases, decreased amplitude, and duration (see Figure 10.6b) compared to normal MUAPs (see Figure 10.6a and Figure 10.6c). Polyphasic MUAPs are observed during submaximal muscle contraction and result from an increased number of action potentials for a given strength of contraction. Myopathic potentials result from a diffuse loss of muscle fiber and indicate the need for extra motor units to perform the work normally done by fewer motor units.[19] Myopathic MUAPs are polyphasic and are most often seen in human with primary myopathies such as myotonia-like syndromes, periodic paralysis, myositis, botulism, and myasthenia-like syndrome[16] and sometimes in early and incomplete dennervation.[20] Also, myopathic potentials have also been reported in steroid-induced myopathies resulting from equine Cushing's syndrome and membrane-defect myopathies.[16] However, very limited data exist in horses with muscle pathology, but polyphasic MUAPs have been recorded in horses with hypocalcemia and hypomagnesemia states (see Figure 10.6b).[13]

Neuropathic or Neurogenic Spontaneous Activity

Neuropathic potentials are MUAPs of decreased frequency and longer duration than myopathic potentials and may he seen during minimal and maximal muscle contraction (see Figure 10.6c). Thus, fewer MUAPs of increased amplitude are observed than expected for the strength of contraction. This is more noticeable during maximal contraction and produces a "sputtering" or "motor boat" sound. These potentials were most often present in primary neuropathies, such as suprascapular and radial nerve paralysis, in which collateral reinnervation has occurred. Neurogenic spontaneous activity has been recorded from the long head of the triceps muscle in horses with hypocalcemia and hypomagnesemia (see Figure 10.6c).[13]

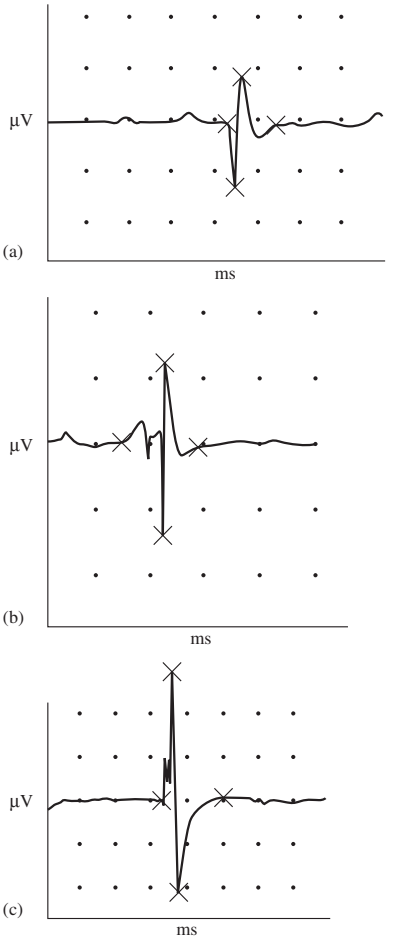


Figure 10.6. Electromyograph from (A) the subclavian muscle of an adult horse showing a normal single tri-phasic motor unit action potential (MUAP); (B) from the vastus lateralus muscle of a horse in a hypocalcemic and hypomagnesemic state showing a polyphasic (6 phases) myopathic MUAP, and (C) from the triceps brachii muscle in a horse in a hypocalcemic and hypomagnesemic state showing a single neuropathic MUAP. Each division represents 200 μV [*y*-axis] and 5 milliseconds [*x*-axis]. Reprinted with permission from Wijnberg JD, van der Kolk JH, Franssen H, et al. 2002. Electromyographic changes of motor unit activity in horses with induced hypocalcemia and hypomagenesemia. Amer J Vet Res 63:849–56.

Fibrillation Potentials

Fibrillation potentials are the most commonly observed abnormal spontaneous potential on electromyographic examination. These spontaneous discharges often sound like "frying eggs," "crinkling cellophane," "frying bacon," or "rain on a tin roof" and have an initial positive deflection of 100–300 μV in amplitude and are 2 to 4 ms in duration in human. They are di- or triphasic and strongly suggest muscle denervation, but have been observed in polymyositis, muscular dystrophy, and botulism. The exact origin of these potentials is uncertain, but they are thought to be spontaneous discharges resulting from the release of acetylcholine from hypersensitive denervated muscle fibers. They may also be secondary to muscle necrosis, muscle inflammation, and focal muscle degeneration. However, a few fibrillation potentials have been observed in normal healthy muscle, but they are usually not reproducible in other areas of the muscle. The onset of fibrillation potentials following denervation depends upon the size of the animal (i.e., the larger the animal, the later the onset of fibrillation potentials). They have been reported to occur between 5 and 16 days after denervation in the dogs and human. We have observed fibrillation potentials 4–10 days after nerve injury in the horse. Furthermore, a recent report showed the presence of fibrillation potentials in horses with hypocalcemia and hypomagnesemia.[13] These fibrillation potentials were measured to range from 12 to 155 μV in amplitude and have duration of 1–10 ms and were shorter in duration than those reported in human.[12] Fibrillation potentials are most often seen in conjunction with positive sharp waves and are indicators of denervation. They increase, then decrease in amplitude as the muscle atrophies; they cease upon complete muscle atrophy, once fibrous connective tissue and fat have totally infiltrated the muscles. Fibrillation potentials occurring alone denote a more severe disease process than does the presence of positive sharp waves alone. Fibrillation potentials are helpful in diagnosing and evaluating the length of the time muscle denervation has been present, and serial examinations are important in assessing clinical prognosis muscle atrophy. A decrease in amplitude and duration over time carries a poor prognosis, whereas, a decrease in the presence of fibrillation potentials followed by the recording of MUAPs suggests reinnervation, which carries a favorable prognosis.

Positive Sharp Waves

Positive sharp waves are potentials in which the primary deflection is in the downward direction and is followed by a lower-amplitude longer-duration negative deflection (see Figure 10.2). This waveform has been described as resembling a saw tooth. Positive sharp waves occur with muscle denervation and muscular diseases such as myositis, exertional rhabdomyolysis (tying-up syndrome), and spinal shock in human. Sometimes, positive sharp waves are observed in association coincident with or shortly after insertional activity and persist after electrode placement. If more than two positive sharp waves are observed after insertional activity, it may indicate early denervation. We have observed positive sharp waves in denervated muscle secondary to chronic exertional rhabdomyolysis, myotonia, protozoal myeloencephalitis, laryngeal hemiplegia, suprascapular nerve injury, and compressive myelopathies. Also, a recent report described quantitative positive sharp waves in horses with hypocalcemia and hypomagnesemia.[13] Positive sharp waves in that study ranged from 13 to 261 μV in amplitude and had a duration ranging from 1.46 to 12.78 ms, which was shorter than that recorded in humans.[12] These potentials can be observed singly or in trains and may sound like "machine gun fire." Their origin is uncertain, but may be associated with hyperexcitable muscle cell membranes. As the muscle cell becomes denervated, it adds more acetylcholine receptors and becomes hyperexcitable.

CRDs and Myotonic Potentials

CRDs (bizarre high-frequency potentials) and myotonic potentials are potentials observed less frequently in the horse. Both of these potentials are repetitive MUAPs induced by insertion of the needle electrode or percussion of muscle. The CRDs are shorter in duration and end abruptly (see Figure 10.7) compared to myotonic potentials, which wax and wane in amplitude and duration (4–5 s) and sound like a "dive bomber" (see Figure 10.8). Both CRDs and myotonic potentials are associated with hyperexcitable muscle membranes. CRDs have a fixed amplitude and frequency, and the initial deflection can be either positive or negative. The firing frequency has been reported to range from 50 to 150 Hz. The CRDs are seen in amyotrophic lateral sclerosis spinal muscle atrophy, myotonic syndromes, and polymyositis.[20] In horses,

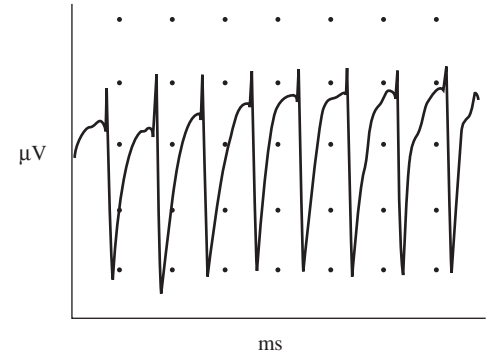


Figure 10.7. Electromyographic recording from the long head of the triceps brachii muscle of an adult horse in a hypocalcemic and hypomagnesemic state. Notice the complex repetitive discharges or neuromyotonia. Each division represents 100 μV (*y*-axis) and 5 milliseconds (*x*-axis).

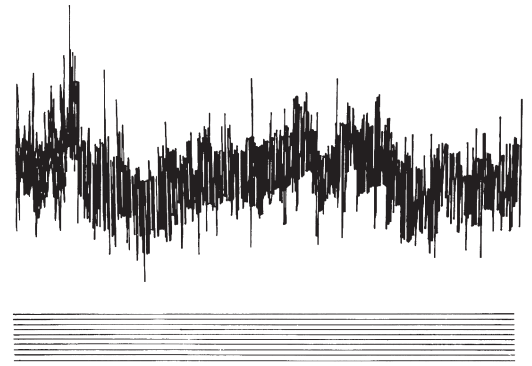


Figure 10.8. Electromyographic potential from the middle gluteal muscle from a foal with myotonia congenita. Note the repetitive waxing and waning discharges or myotonic potentials.

CRDs have been recorded in rhabdomyolysis and myotonia,[21] hypocalcemia and hypomagnesemia,[13] laryngeal hemiplegia,[22] hyperkalemic periodic paralysis,[23,24] equine motor neuron disease,[15,25] and rarely in normal horses.[14]

Myotonic potentials are repetitive discharges with a firing frequency of approximately 20–50 Hz with an initial positive deflection. Warming up or cooling down of muscles influence the occurrence of myotonic discharges.[11] They have been recorded in horses with myotonia congenita[21,26] (see Figure 10.8), myotonia dystrophia,[27] and hyperkalemic periodic paralysis,[10,23,24,28] and they may reflect hyperexcitability due to abnormal electrolyte transport in the muscle.

ABR TESTING

Brainstem auditory-evoked potentials (BAEP) are measured during ABR testing and are neuroelectric potentials arising from the eighth cranial nerve and its projections along the brainstem. These potentials are measured using platinum or stainless steel electrodes placed in the subcutaneous tissue of the head of horses in response to acoustic stimulation (click stimulator placed in the ear or over the ear with headphones). These evoked potentials appear as waves arising within the first 10 ms after the delivery of an acoustic stimulus. In horses, five to seven waves are recognized and designated as Roman numerals I through VII; of these, waves I through V are the most commonly seen in horses (Figure 10.9). Each peak corresponds to different anatomic generator sites along CN VIII and its projection along the brainstem.[29,30] Wave I is generated by bipolar neurons of the ipsilateral eighth cranial nerve. Wave II may also be generated partly by the eighth cranial nerve, whereas waves III and IV are thought to be generated by the region of the trapezoid body in the pons and lateral lemniscus, respectively. Wave V is generated from the region of the caudal colliculus in the midbrain. Peaks VI and VII arise from generators in the medial geniculate body in the thalamus and auditory radiations, but these peaks are rarely present in horse. A wide range of clinical applications of ABR testing in human beings have been described. However, the clinical use of ABR testing in horses has been limited but is an ancillary method of assessing auditory function and neurologic disorders involving the brainstem. Since the state of arousal of the patient does not affect BAEPs, testing can be done on sedated and anesthetized patients without degradation of the signal.

Instrumentation

Commercially available electromyographs have settings and components available to do ABR testing. The general equipment and procedure includes a

click stimulus produced by a square wave generator (square wave, alternating polarity at a rate of 20 clicks per s) delivered to the ears by a pair of insert earphones or headphones using hearing aid receivers with a frequency response of 100–6000 Hz. Impedance matching transformers are used to match the click generator to the earphones to minimize energy loss. The earphones are inserted into the horse's external auditory canals and held in place with wax ear plugs. The wax plugs occlude the ear canal, reduce the loss of acoustic energy, and attenuate background noise. Platinum or stainless steel needle EEG electrodes (12 mm in length) are inserted subcutaneously with the active (inverting) electrode placed over the ipsilateral (to the stimulus) zygomatic process of the temporal bone near the base of the pinna and the reference (non-inverting) electrode inserted at the vertex over the parietal suture just rostal to the site where the temporalis muscles diverge from the midline and the ground positioned over the bony part of the caudal aspect of the external occipital protruberance or wing of the atlas.[31,32] Electrodes are connected to an amplifier near the horse's head. An upward deflection is produced on the computer screen in response to electrical activity at the vertex. Electrode impedance is between 1000 to 10,000 ohms. The BAEPs are recorded with a high-pass filter set at 0.08 Hz and a low-pass filter set at between 2.0 and 3.2 kHz. Display gain is varied to produce the best record. The differential voltage is sampled for 10 ms after each click, digitized, and summed for approximately 500–1000 sweeps to produce the desired evoked waveform. The BAEPs can be recorded over a 70-dB range (30–90 dB), with the best response seen between 60 and 90 dB. Horses can be examined while they awake, with or without mild sedation (xylazine hydrochloride [0.4 mg/kg, IV], detomidine hydrochloride [0.013 mg/kg, IV]),[32] or while anesthetized.[31] If the horse is tested while it is awake, each ear is stimulated, and resultant waveforms are recorded independently. If the patient is examined while it is anesthetized, the uppermost ear is done first, then the lower ear.[31]

Interpretation of ABR

Five peaks are commonly observed and are considered analogous to waves I through V seen in human beings. Mean latencies have been reported in the literature for normal horses.[31] ABR testing can be used clinically in horses with a head tilt to evaluate brainstem or peripheral nerve injury[33] in horses with trauma, to verify the presence of hearing loss especially in horses with congenital hearing deficits[5,34] (see Figure 10.9), middle or inner ear infections, and stylohyoid osteomyelitis. It may also be helpful in the diagnosis and prognosis of traumatic, infectious, or inflammatory brainstem lesions such as vascular infarcts or anomalies, ischemic fibrocartilaginous emboli, basisphenoid–basioccipital bone fracture, and protozoal myeloencephalitis. Quantitative and qualitative characteristics of the ABR-generated waveforms can be assessed. Persistent prolonged latencies suggest retrocochlear or conductive pathologies. Interaural latency differences of wave V may suggest unilateral brainstem disease, except when cochlear disease is present. Qualitative ABP changes are of greater use in equine medicine because quantitative measures of normal and abnormal horses are limited. In human beings, qualitative changes such as peak presence, waveform morphologic characteristic, and response stability are of greater use in the diagnosis of central disorders, particularly acoustic neuromas and demyelinating diseases, which are not well characterized in horses. Limitations of ABR testing include a dependence on cochlear function, susceptibility to extraneous noise

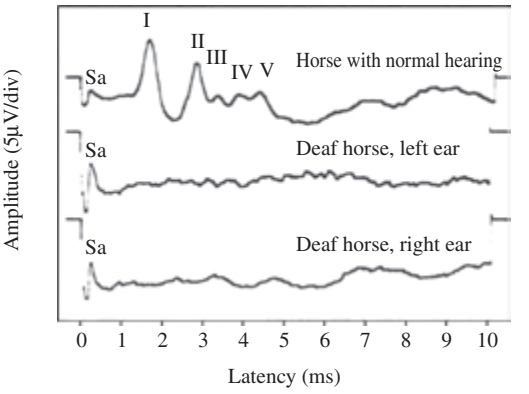


Figure 10.9. Brainstem auditory evoked response from a horse with normal waves I-V and bilateral deafness. Reprinted with permission from Harland MM, Stewart AJ, Marshall AE, et al. 2006. Diagnosis of deafness in a horse by brainstem auditory evoked potential. Can Vet J 47:151–4.

that may affect waveform morphology, and limits of the machinery in excluding 60-cycle interference. Recently, ABR was used to confirm congenital deafness in a blue-eyed, sorrel, white overo American Paint horse (see Figure 10.9).[34] Also, ABR was used to show a subtle left to right interaural latency difference of waves I, III, and V in a pony that was suspected to be struck by lightning.[33]

ELECTROENCEPHALOGRAPHY

EEG is a relatively simple and noninvasive neurophysiological technique, which is defined as the graphic recording of the rhythmic bioelectrical activity arising predominantly from the cerebral cortex. It has been extensively used and reviewed in human beings and small animals,[35–39] but less work has been done in horses.[40–63] This section presents a description of its electrophysiological basis, montage, and expected patterns, so that one may gain a better understanding regarding its use, interpretations, and limitations.

Since its first introduction in 1929 by Hans Berger, a German neuropsychiatrist, EEG has been extensively used to study brain function and to provide important diagnostic information in human patients with intracranial neurological disorders. EEG is most useful in the investigation and management of human patients with epilepsy, in particular in establishing disease progression, need for treatment, and probability of recurrence.[35] EEG was first introduced in veterinary medicine in the 1960s and was initially used as a laboratory tool both in small and in large animals.[61,64–75] Similar to human epileptology, several studies have demonstrated the validity and importance of EEG as a diagnostic tool in canine epilepsy.[76,77] However, since the introduction of advanced diagnostic imaging techniques to detect any structural abnormalities in the brain and the skull, such as computerized tomography (CT) and magnetic resonance imaging (MRI), the use of EEG in small animal medicine has been somewhat limited and may not be included in the work-up of many neurological cases.[78] However, a recent study demonstrated the lack of sensitivity of MRI in diagnosing dogs with focal epilepsy, reinforcing the need of EEG to establish diagnosis and prognosis in epileptic patients.[79] In large animals, EEG was initially used by implanting surgically electrodes in the skull, in particular to study natural sleep and its disorders.[44,46,64–69,74] More recently, EEG has been used to monitor electrical activity of the cerebral cortex to evaluate central nervous effects and antinociceptive efficacy of different anesthetic agents, and to monitor anesthetic depth during general anesthesia in horses.[43,49–53,57,58,60,80,81,82,83] In contrast, there are few studies reporting the clinical use of EEG in horses.[42,54,55,84–86] Diagnosing seizures in horses can be very challenging; one of the main difficulties lies in the rapid return to normal activity without persistent neurological deficits coupled with a small number of facilities capable of imaging the equine brain. For instance, MRI is not readily available to accommodate an equine adult head, and CT scan is less sensitive than MRI to image soft-tissue structure, such as the brain. Thus, EEG should be considered as part of the diagnostic work-up for patients presented with abnormal behavior, collapse, or seizure-like activity. Indeed, EEG is a good tool to diagnose intracranial disorders in horses presented with a history of seizure-like activity, with a specificity of 70% and sensitivity of 100%, and with a positive neuroanatomic correlation in 70% of the cases.[54] Similar to findings in small animals, EEG is more helpful in making a diagnosis of epilepsy associated with intracranial disorders compared to physical and neurological examinations and cerebrospinal fluid analysis.[54,87] However, EEG is a complementary test to, rather than an alternative to, other diagnostic tests and may allow the clinician to construct a list of differential diagnoses that help identify the cause of the seizures in the light of the history, neurological examinations, and other diagnostic tests. The main limitations of this electrodiagnostic test are related to the facts that: (1) only electrical activity arising from the superficial part of the cerebral cortex is recorded; (2) it requires extensive expertise from the clinician to interpret the reading; (3) it is mostly limited to some large private practices and neurological referral institutions.

Electrophysiological Basis of EEG

The complete description of the electrophysiological process underlying the generation of EEG signals is beyond the scope of this chapter, and the reader can refer to a detailed review on this topic.[88]

If two electrodes are placed on the scalp where the cerebral hemisphere is close to the surface, spontaneous (without any stimulation) electrical activities from the cerebral cortex can be recorded with the use of appropriate amplifier-recording

systems. These activities are primary the algebraic summation of excitatory and inhibitory postsynaptic potentials (PSPs) from a large population ($>10^5$) of cortical neurons.[89] When a PSP (either excitatory or inhibitory) occurs, the release of neurotransmitters from the presynaptic neuronal membrane allows selective movements of ions through the postsynaptic terminal of the neuron. These transmembrane currents result in transient redistribution of positive and negative charges in both intracellular and extracellular spaces, with the generation of dipoles and subsequently of extracellular field potentials.[88,89] It is thought that the formation of extracellular field potentials recorded by the surface electrode originates mostly from pyramidal cell dendrites located within a 2-mm depth of the cerebral cortex.[90] This electrical activity may also be modified by deeper structures such as the brainstem, reticular activating system, and thalamus. Summation of large numbers of PSPs will result in the generation of the EEG signal, with a typical voltage ranging from 3 to 300 μV, recurring at frequencies of 0.5 to 40 Hz.

Montage

The EEG machine is a polygraph, which consists of inputs for multiple electrodes, and of amplifiers which increase the voltage of the electrodes connected from the head to the inputs of the amplifiers. Electrodes consist of platinum needle electrodes placed subcutaneously in the scalp or of small silver disk electrodes applied to the skin surface of the head. There are various methods for the placement of electrodes on the scalp, so-called "montages." These electrodes are placed symmetrically in the scalp over the frontal, occipital, and parietal areas, and a ground electrode is also necessary. The difference of potential detected between pairs of electrodes (or between an electrode and its reference) is amplified and then recorded on continuously moving paper with a number of pen-writers or heat-writing styluses. This same input can also be digitalized for electronic analysis, display, and storage. The direction of the movement of the pen is determined by the polarity of the electrodes relative to each other.[90] By convention, an upward deflection of the pen occurs when the recording electrode becomes negative relative to the reference electrode. Conversely, a downward deflection of the pen occurs if the recording electrode is positive with respect to the reference electrode. The montage is the arrangement of reference and recording electrodes placed over the brain. The two main montages are reference and bipolar (see Figure 10.10). The reference montage contains the reference electrode which is placed over an electrically "inactive" site (vertex lead) and allows the determination of absolute voltage and polarity. However, the common reference site is never completely inactive and thus contributes to the output signal and can become contaminated.[89] Bipolar montage links a serial pair of active electrodes (one of which is considered as the "exploring" and the other one as the "reference" electrode) in the

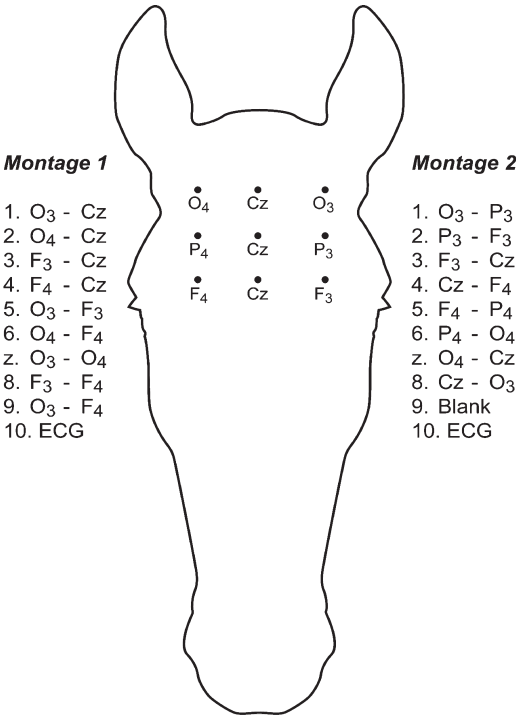


Figure 10.10. Drawing of the forehead of a horse illustrating electroencephalographic electrode positioning and the 2 montages used: bipolar left-to-right, back-to-front montage (1) and bipolar circular montage (2). O, occipital; P, parietal; F, frontal; C, central. Reprinted with permission from Lacombe V, Podell M, Furr M, et al. 2001. Diagnostic validity of electroencephalography in equine intracranial disorders. J Vet Intern Med 15:385–93.

transverse or coronal direction. Since each electrode records electrical activity from a small localized area underneath, the electrodes can be configured in several bipolar arrangements, which is necessary for the localization of epileptic foci. With such a montage, one can compare the potentials generated by the left occipital region with those of the right occipital cortex, the potentials generated by the left frontal cortex region with those of the right frontal area, and the potentials generated by the left side with those of the right side.[5] Localization of discrete focal abnormalities in bipolar montages is usually accomplished by locating the common electrode of two adjacent pairs, at which the pen deflection shows a reversal of polarity ("phase reversal"). Other advantages of bipolar recording include elimination of the possibility of a contaminated reference and prevention of problems that can arise from unbalanced amplifier input with common reference. On the other hand, widely distributed potentials may be distorted, and voltage and polarity determinations are always relative to electrode placement.[89] Since they provide complimentary information, the use of multiple montages including bipolar and referential types and a combination of both should be used during each EEG recording. The EEG examination should also be performed in a quiet, relatively dark environment. Time of recording will depend on the condition of restraint of the patient and the level of cooperation, but a minimum of 20-min recording is recommended.

Patient Restraint

EEG may be performed on awake, sedated animals, or anesthetized horses, and the condition of recording greatly depends on the preference of the clinician. In humans and small animals, recordings on awake patients are optimal because the use of sedation and general anesthetic agents influence EEG patterns by altering cortical activity.[39] However, general anesthesia will significantly reduce artifacts caused by head, ear, and eye movements of the patient and those caused by auditory and visual stimuli. To easily identify such bioelectrical artifacts on awake or lightly sedated horses, some clinicians record simultaneously electro-oculographic, electromyographic, and electrocardiographic activities as well as the horse's behavior. EEG segments can then be separated from artifacts.[56] Furthermore, photic and auditory stimulation may be applied as activation methods, to enhance preexisting abnormalities or to induce abnormal signals on a relative normal background. The use of EEG as an ambulatory technique has also been described with continuous recording over 18 h in animals in their environment.[45] However, since recording on alert animals is usually challenging, sedation or general anesthesia is usually preferred or required. Thus, a standardized protocol should be used, and cautious interpretation of the EEG recording obtained under such condition is crucial to avoid over-interpretation of drug-induced changes in EEG background. For instance, xylazine-sedated horses display in general hypersynchronous EEG, with a dominant pattern of high-voltage and slow-wave activity, and ketamine administration 3 min after xylazine injection caused an increase in high-voltage, slow-wave activity.[83] The depth of anesthesia also can interfere with the electrical background. EEG recordings in ponies during volatile anesthesia changed with the depth of anesthesia from low-voltage, fast-wave activity to high-voltage, slow-wave activity.[41] Inhalation and intravenous anesthetics also have the potential to increase the threshold for seizures in horses, thus reducing or masking potential epileptiform activity on EEG recording. For instance, antiepileptic properties of halothane and isoflurane have been demonstrated in humans.[91] Furthermore, benzodiazepines, which are commonly used for immediate control of seizures, are potent anticonvulsant. Finally, because of its dissociative effect and of its potential antagonist action on *n*-methyl-D-aspartate (NMDA) receptors, ketamine appears to have both proconvulsant and anticonvulsant properties in humans.[91] Nonetheless, recording EEG under anesthesia offers some diagnostic advantages. In particular, EEG recording provides a high-quality recording with a stable baseline by reducing the number of artifacts. Furthermore, the use of anesthesia may sometimes unmask asymmetry, waveform distortions, and abnormal incidence of spindles, waveforms not necessarily seen in the alert patient.[37,77]

Interpretation of EEG

There are two main methods: simple visual inspection and the automated computerized analysis. The quantitative computerized method analyses the EEG signal in the frequency domain and provides power spectrum, bispectral analyses, and cortical mapping capabilities.[92] This quantitative analysis has been used in equine anesthesiology to evaluate

the anesthetic depth,[60,81,82,93] but artifacts or paroxysmal discharges may be missed during this global analysis. Thus, visual inspection has been the time-favored approach, but it requires a great deal of experience due to the subjective nature of its interpretation.

The principal of visual inspection is to assess the frequency and amplitude and the presence or absence of asymmetrical patterns, of paroxysmal activity, and of artifacts. Frequency is defined as the number of observed events (changes in the direction of voltage) per second and amplitude of the wave refers to the magnitude of changes between peaks. Alternatively, a semiquantitative visual analysis may be used to remove some of the subjectivity.[54,94] In each category (frequency, voltage, asymmetry, and paroxysmal activity), a score of 0 or 2 is assigned when normal or the most abnormal activity is observed, respectively. By default, intermediate range activity between normal and most abnormal is then given the intermediate value (score of 1) (see Table 10.2).

Normal EEG Patterns: Background, Artifact, Normal Values

The establishment of normal values, universally recognized, is difficult because frequency and amplitudes are state dependent (e.g., awake, drowsy, sleeping, sedated, or anesthetized). Furthermore, cortical activity is also influenced by physiological states. For instance, interpretation of EEG in foals is difficult because large variations on EEG recording may be observed dependent on the stage of maturation of the brain. Furthermore, the age at which cerebral maturation occurs is unknown in horses. In most mammalian species, alpha rhythm (electrical activity with a frequency of 8–13 Hz) has been considered the most predominant pattern observed in a mature brain.[59] In neonatal foals, the normal patterns include high-voltage, slow-wave activity.[54,59] As neuronal maturation occurs with an increased complexity and divergence of the dendritic network, faster and lower voltage activity becomes more predominant on EEG recording. Therefore, it is critical for the clinician to take into consideration the state of awareness and age of the patient, and to know what is considered a normal EEG tracing under such condition.

In order to accurately interpret the EEG pattern and to potentially recognize pathological changes, one must first evaluate the background (for frequency, amplitude, and symmetry) and identify normal transients and potential artifacts. Frequently encountered artifacts include muscle potential artifacts, movement artifacts, and respiratory artifacts. To obtain a high-quality recording of the baseline, it is critical to detect early and if possible to eliminate these artifacts. Generally, artifacts such as ocular movements and facial muscle twitches produce symmetric and asymmetric low-voltage, slow-wave activity, respectively.[5] When muscle potential artifacts are detected during the recording, the skin and muscle underlying the electrodes should be desensitized with 2% mepivacaine by subdermal injection. Normal waveforms that may be misleading include spindles and burst suppression, which are normal transient events observed during sedation or anesthesia. Spindles are repetitive sinusoidal waves, and burst suppression refers to isoelectric periods (e.g., electrical silence) interrupted by brief intervals of high-amplitude activity, which are usually observed only during deep anesthesia.[92] Vertex waves are

Table 10.2. Scoring System for Semi-quantitative Analysis of the Equine EEG Performed Under General Anesthesia, Developed at the Ohio State University[54]

Measurement		Low	Moderate	High
Frequency	Score	2	0	1
		<8 Hz	8–13 Hz	>13 Hz
Voltage	Score	1	0	2
		<25 μV	25–50 μV	>50 μV
Asymmetry	Score	0	1	2
Paroxysmal activity	Score	0	1	2
		<25%	25–50%	>50%

observed in response to stimulation and do not have a spike component, which allow them to be differentiated from paroxysmal waveforms.[90]

Normal EEG background in the awake alert horse, which was first described in 1968, consists of a dominant waveform of low voltage (8–15 μV) and fast-wave activity (18–30 Hz) (Table 10.3).[55,59] Usually, this activity is superimposed over a low-to-medium voltage (10–40 μV) and slow-wave activity (5–10 Hz). Normal values have also been established in adult horses under general anesthesia and include a frequency of 8–13 Hz and a voltage of 25–50 μV (see Figure 10.11 and Table 10.3).[54] In sedated foals, the observed pattern includes high-voltage (50–200 μV) and slow-wave activities (1–2 Hz).[54,59]

It is also important to recognize normal EEG patterns during various states of sleep, although there is limited information in horses.[64,68,95] As in other species, slow-wave sleep is characterized by synchronized high-voltage (100 μV) and slow-wave activities (2–4 Hz) in normal adult horses, which is similar to the pattern in tranquilized horses. Paradoxical sleep is characterized by desynchronized low voltage and fast-wave activity, which resembles the patterns of alert wakefulness. During this period, the horse is recumbent; eye movements, frequently accompanied by ear and leg movements and even by vocalization, are observed.[63,65]

Abnormal EEG Patterns Associated with Diseases

EEG has been used to investigate horses presenting with a history of seizures, abnormal behavior, collapse, narcolepsy and also horses affected with cerebellar disease and encephalitis.

Accurate interpretation of the EEG recording can provide usual information in regard to the presence (or absence) of cerebral disease and its nature (acute vs. chronic; focal vs. diffuse; inflammatory vs. degenerative). One should assess the background for abnormal frequency and amplitude, for the presence of asymmetrical patterns between regions, and for the presence of paroxysmal activity. The most common abnormalities associated with cerebral diseases are the change in either amplitude or frequency, or both; and the following general principles can be applied[73]:

1. Low-voltage, fast-wave activity along with paroxysmal spikes may occur with ongoing irritative processes such as seizures or inflammation (see Figure 10.12).
2. High-voltage, slow-wave activity may indicate death of neurons in diseases such as brain abscess, neoplasia, and cerebrocortical necrosis. For example, such pattern was observed in sheep and cattle with experimental cerebrocortical necrosis and in foals with hypoxic ischemic encephalopathy.[54,96,97]
3. However, neither change is pathognomonic of a particular disease, but rather reflects the nature of the pathologic process occurring (e.g., inflammation or degeneration).
4. Localized EEG changes may indicate focal cortical disease such as infarcts, hemorrhage, early tumor, or abscessation (see Figure 10.13).
5. Generalized EEG changes may indicate a diffuse cortical or subcortical disease such as infection,

Table 10.3. Amplitudes and Frequencies Observed in Normal Electroencephalographic Patterns from Awake and Sedated Adult Horses[59,83]

		Normal Patterns	
		Voltage (μV)	Frequency (Hz)
Awake	Primary pattern	8–15	18–30
	Secondary pattern	10–40	5–10
Sedated with xylazine	Dominant	10–70	1–3 [83]
		10–80	10–15[59]
		10–90	0.5–4[59]
		5–30	25–40[59]
Sedated with acetylpromazine	Primary pattern	5–40	25–40[59]
	Secondary pattern	5–10	1–4

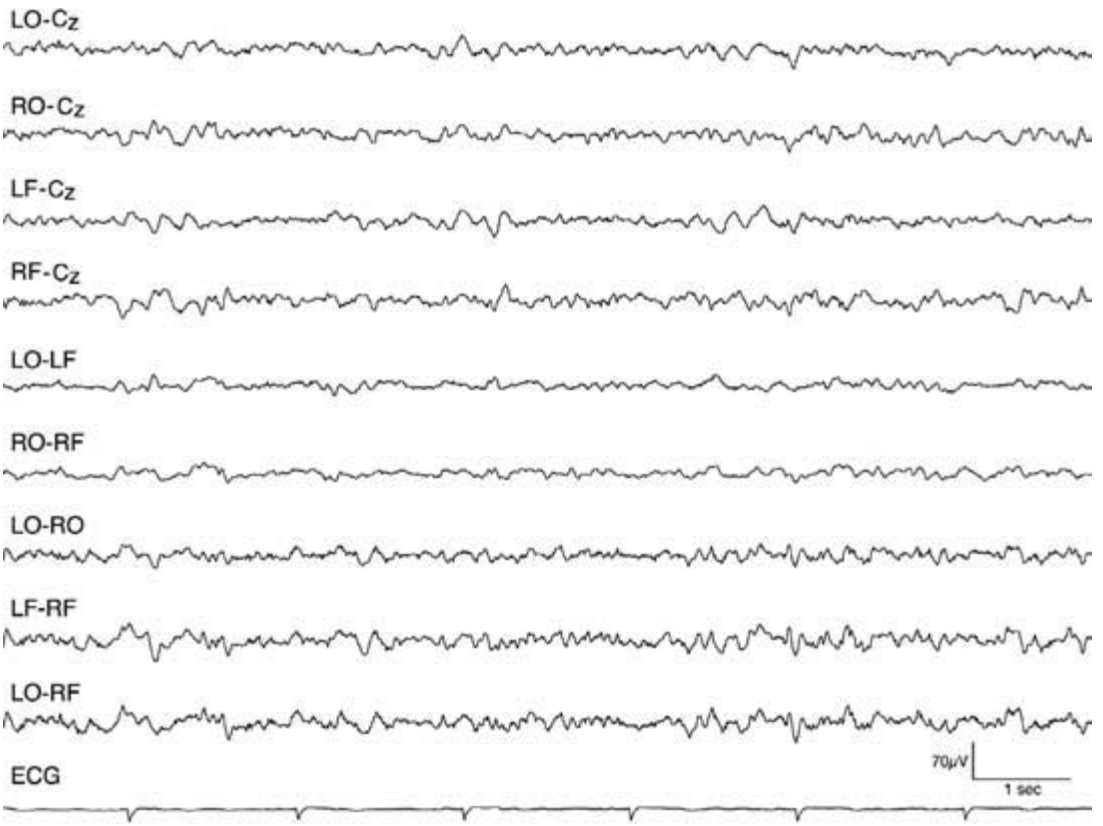


Figure 10.11. A normal adult equine electroencephalographic recording made under general anesthesia with a bipolar left-to-right, back-to-front montage. A moderate voltage (8–13 Hz) and moderate frequency (25–50 mV), without any asymmetry or paroxysmal activity were present. L, left; R, right; O, occipital; F, frontal; ECG, electrocardiogram. Reprinted with permission from Lacombe V, Podell M, Furr M, et al. 2001. Diagnostic validity of electroencephalography in equine intracranial disorders. J Vet Intern Med 15:385–93.

trauma, space-occupying lesions (hydrocephalus, tumor), idiopathic epilepsy, or a systemic metabolic illness (hepatic encephalopathy and hypocalcemia). For example, generalized slower activity with a remarkable high voltage (100–200 μV) has been reported in dogs and calves with hydrocephalus.[98,99]

6. EEG reflects ongoing pathological changes; thus, serial recording may be helpful as a prognostic indicator for following the response to therapy and disease progression.

One of the most common indications for performing an EEG is to confirm the clinical diagnosis of epilepsy, which is defined as a clinical manifestation of excessive and/or hypersynchronous abnormal neuronal activity in the cerebral cortex, and to potentially determine its etiology. EEG is the most important paraclinical test in human suffering from epilepsy, and this diagnostic test has also been shown to be useful in dogs and horses with seizures.[54,76,77] In epileptic patients, increase toward low-voltage, fast-wave activity or high-voltage, slow-wave activity may be seen.[37] In addition, epileptiform paroxysmal activity appears on the majority (40–90%) of EEGs recorded on epileptic patients.[54,77,100] The proximity of a seizure to the EEG examination may also influence the amount of

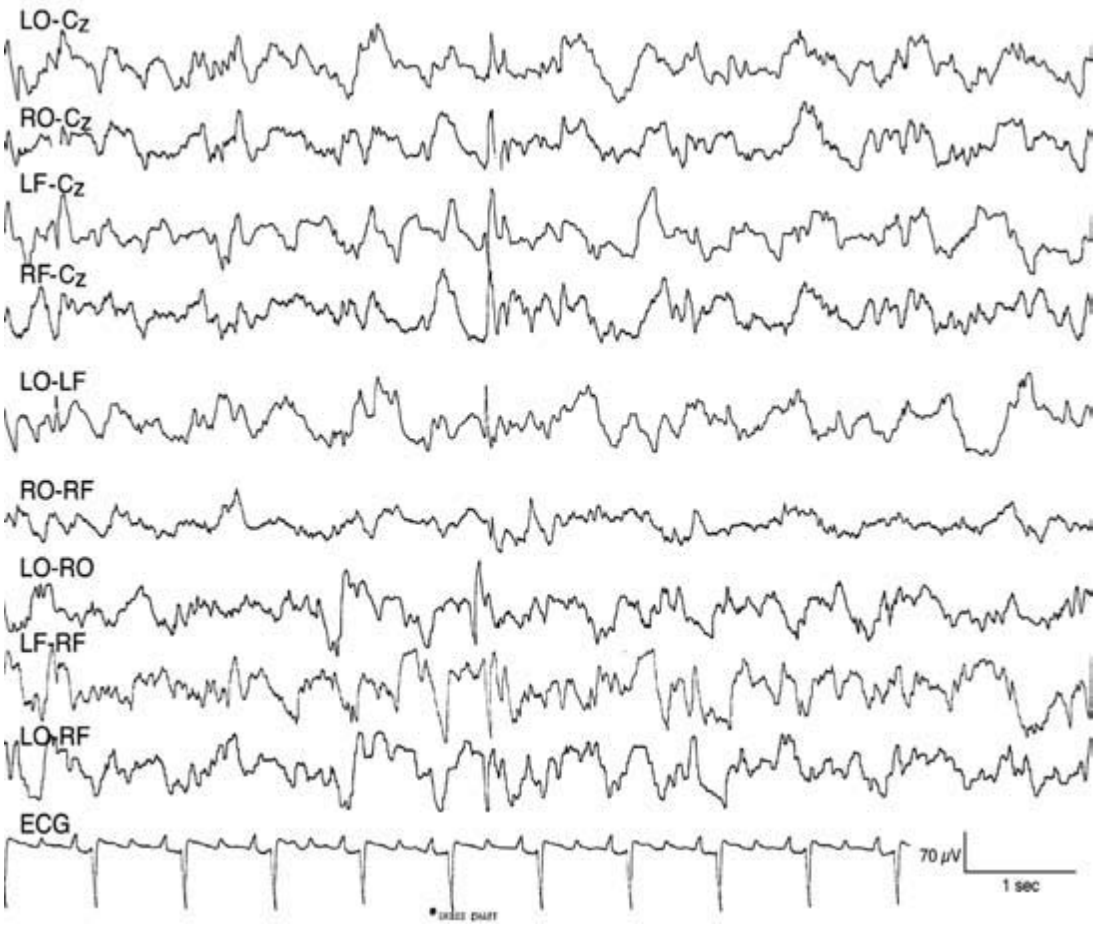


Figure 10.12. Electroencephalographic (EEG) recording made under general anesthesia from a 1-day-old filly that presented for lack of nursing and intermittent tremors. This recording revealed diffuse high-voltage slow waves and focal discrete paroxysmal discharge activity. Multifocal paroxysmal activity was seen on the remaining EEG recording. Reprinted with permission from Lacombe V, Podell M, Furr M, et al. 2001. Diagnostic validity of electroencephalography in equine intracranial disorders. J Vet Intern Med 15:385–93.

epileptiform activity present in the EEG.[76] These activities are defined as abnormal paroxysmal transient events, consisting of spikes or sharp waves, isolated or followed by a wave, spike and wave, or polyspike and wave complexes.[76,100] Both generalized and focal epileptiform activity have been recorded in epileptic horses.[54] Although epileptiform paroxysmal activity has been associated with the pathophysiology of seizures, it is important to realize that failure to record epileptic activity does not automatically rule out epilepsy, since the use of tranquilizers may increase the threshold for seizures and since the window of recording may not have been long enough to record interictal paroxysmal epileptiform discharges. To avoid this, frequent and prolonged sophisticated EEG monitoring is routinely performed in humans, but it is not practical in large animals. Therefore, one should consider repeating EEG examination in an animal suspected of having epilepsy and for which the first EEG recording was normal.

One could also consider using EEG in the investigation of other neurologic disorders such as in cases of suspected cerebral inflammatory processes. The

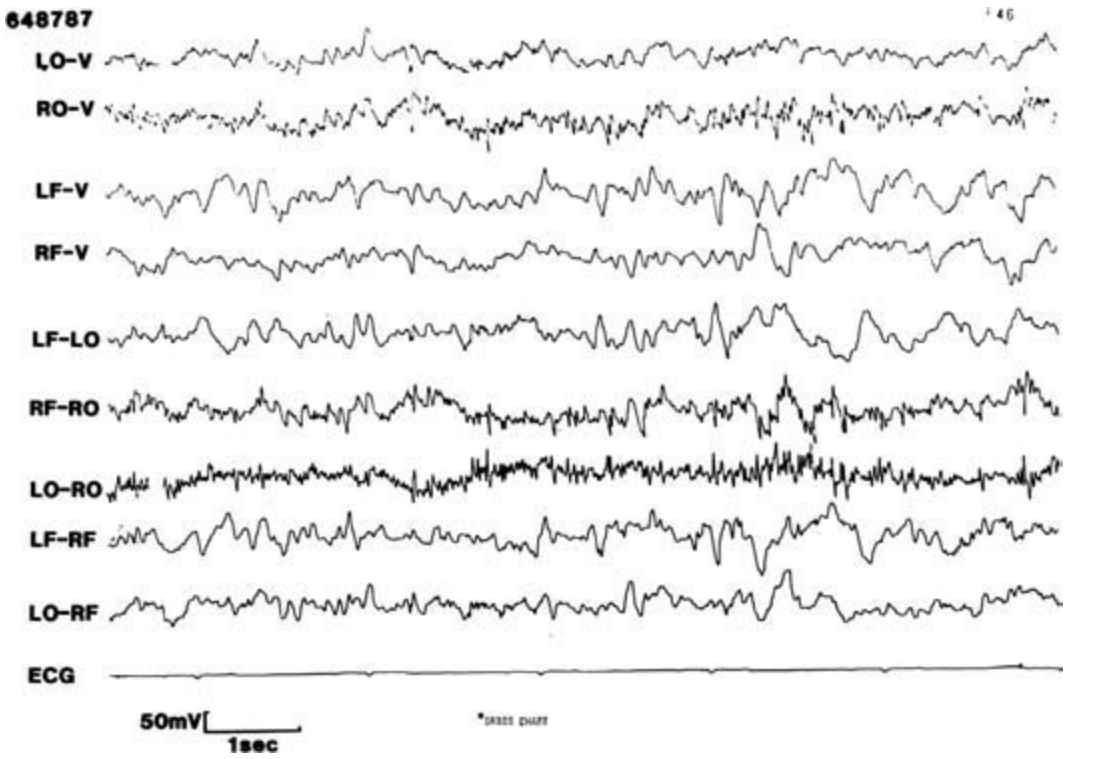


Figure 10.13. Electroencephalograph from a horse with a space-occupying mass in the left frontal area of the brain under general anesthesia. The generalized high-voltage, low-frequency wave and asymmetry of the left cortex are notable. L, left; R, right; O, occipital; F, frontal; V, vertex, ECG, electrocardiocardiogram position.

EEG has proven to be a very useful tool in the diagnosis of encephalitis and meningitis. For instance, serial EEG recording in horses with experimental West Nile virus encephalitis revealed a generalized abnormal electrical activity before the development of any clinical sign.[55] Acute case of encephalitis is characterized by high-voltage activities, whereas late stage is characterized by slow voltage (1–5 μV) and slow-wave (3–4 Hz) activities in the awake horse. Furthermore, EEG in a 11-month-old filly affected by equine encephalitis was characterized by periodic episodes of generalized synchronous high-voltage, slow-wave activity with generalized seizure activity.[85] In a few cases of equine protozoal myeloencephalitis presenting with seizures, EEG demonstrated a higher generalized voltage than normal and was used to establish the neurophysiologic and anatomic basis for the seizure activity.[42] Brain abscesses frequently show localized slow-wave activity superimposed by some sharp waves. In a case of sinonasal adenocarcinoma extending into the right cranial vault and causing central nervous system disease, the EEG pattern included low-voltage irregular delta wave (e.g., activity <4 Hz), which is characteristic of asymmetric space-occupying mass.[84] Although EEG is helpful in localizing structural abnormalities, in some instances, the EEG pattern of horses with intracranial masses, such as abscesses, includes generalized continuous high-voltage, slow-wave activity and is not specific as to localization.[54,84] Similar observations have been reported in other species.[36]

Finally, horses suffering from extracranial diseases may have an abnormal EEG recording associated with metabolic disease. For instance, it has been reported in other species that hypothyroidism may produce symmetric low-voltage, medium-frequency activity and that hepatoencephalopathy is

characterized by fast frequencies (5–20 Hz) and medium voltages (15–50 μV). The EEG patterns of hypocalcemia-induced seizures in a foal included diffuse and symmetric slow-wave activity associated with discrete epileptiform activities.[54] Finally, abnormal EEG pattern, including beta activity (e.g., frequency >13 Hz) and numerous triphasic-like waves, was recorded in a horse suffering from ongoing malignant hyperthermia episodes.[101]

REFERENCES

1. Nollet H, Deprez P, Van Ham L, *et al*. 2002. The use of magnetic motor evoked potential in horses with cervical spinal cord disease. *Eq Vet J* 34:156–63.
2. Robert C, Valette JP, Degueurce C, *et al*. 1999. Correlation between surface electromyography and kinematics of the hindlimb of horses at trot on a treadmill. *Cells Tissues Organs* 165:113–22.
3. Stewart CR, Nanedkar SD, Massey JM, *et al*. 1989. Evaluation of an automatic method of measuring features of motor unit action potentials. *Muscle Nerve* 12:141–48.
4. Guld C, Rosenfalck A, Willison RG. 1971. Technical factors in recording. In *Electrodiagnostics and Electromyography*, edited by Licht SL, 452–78. Baltimore: Waverly Press Inc.
5. Andrews FM, Fenner WR. 1987. Indications and use of electrodiagnostic aids in neurologic disease. *Vet Clin North Am Equine Pract* 3:293–322.
6. Henry WH, Diesem CD, Wiechers MD. 1979. Evaluation of equine radial and median nerve conduction velocities. *Am J Vet Res* 40:1406–10.
7. Henry RW, Diesem CD. 1981. Proximal equine radial and median motor nerve conduction velocity. *Am J Vet Res* 42:1819–22.
8. Kimura J. 2001. Techniques and normal findings. In *Electrodiagnostics and Diseases of the Nerve and Muscle: Principles and Practice*, edited by Kimura J, 307–38. New York: Oxford University Press.
9. Mayhew IG, Whitlock RH, de Lahunta A. 1978. Spinal cord disease of the horse, electromyographic and radiographic studies. *Cornell Vet Suppl* 68:44–62.
10. Robinson JA, Naylor JM, Crichlow EC. 1990. Use of electromyography for the diagnosis of equine hyperkalemic periodic paresis. *Can J Vet Res* 54:495–500.
11. Wijnberg ID, Franssen H, van der Kolk JH, *et al*. 2001. Quantitative analysis of motor unit action potentials in the subclavian muscle of healthy horses. *Am J Vet Res* 63:198–203.
12. Oh SJ. 1998. Needle electromyographic study. In *Principles of Clinical Electromyography. Case Studies*, edited by Oh SJ, 78–120. Baltimore: Williams and Wilkins.
13. Wijnberg ID, van der Kolk JH, Franssen H, *et al*. 2002. Electromyographic changes of motor unit activity in horses with induced hypocalcemia and hypomagnesemia. *Am J Vet Res* 63:849–56.
14. Wijnberg ID, Franssen H, van der Kolk JH, *et al*. 2002. Quantitative motor unit action potential analysis of skeletal muscles in the warmblood horse. *Equine Vet J* 34:556–62.
15. Podell M, Valentine BA, Cummings JF, *et al*. 1995. Electromyography in acquired equine motor neuron disease. *Prog Vet Neurol* 6:128–34.
16. Bowen JM. 1976. Electromyography. In *Applied Electronics for Veterinary Medicine and Small Animal Physiology*, edited by Klemm WR, 188–276. Springfield: Charles C Thomas Pub.
17. Kugelberg E, Petersen L. 1949. Insertion activity in electromyography with notes on denervation muscle response to constant current. *J Neurol Neurosurg Psychiatry* 12:268–73.
18. Kornegay JN, Gorageaz EJ, Dawe DL, *et al*. 1980. Polymyositis in dogs. *J Am Vet Med Assoc* 176:431.
19. Warmolts JR, Engel WK. 1970. A critique of the "myopathic" electromyogram. *Trans Am Neurol Assoc* 95:173–7.
20. Daube JR. 1985. Electrophysiologic studies in diagnosis and prognosis of motor neuron disease. *Neurol Clin* 3:540–1.
21. Beech J, Fletcher JE, Lizzo F, *et al*. 1988. Effect of phenytoin on clinical signs and in vitro muscle twitch in horses with chronic intermittent rhabdomyolysis and myotonia. *Am J Vet Res* 49: 2130–3.
22. Moore MP, Andrews FM, Reed SM, *et al*. 1988. Electromyographic evaluation of horses with laryngeal hemiplegia. *Equine Vet Sci* 8:424–7.
23. Naylor JM, Robinson JA, Crichlow EC, *et al*. 1992. Inheritance of the myotonic discharges in American Quarter horses and the relationship to hyperkalemic periodic paralysis. *Can J Vet Res* 56:62–6.
24. Naylor JM, Jones V, Berry SL. 1993. Clinical syndromes and diagnosis of hyperkalemic periodic paralysis in Quarter horses. *Equine Vet J* 25:227–32.
25. Divers TJ, Mohammed HO, Cummings JF, *et al*. 1994. Equine motor neuron disease: findings in 28 horses and proposal of pathological mechanism for the disease. *Equine Vet J* 26:409–15.
26. Andrews FM, Spurgeon TL, Reed SM. 1986. Histochemical changes in skeletal muscle of four male horses with neuromuscular disease. *Am J Vet Res* 47:2078–83.

27. Hegreberg GA, Reed SM. 1990. Skeletal muscle changes associated with equine myotonic dystrophy. *Acta Neuropathol* 80:426–31.
28. Spier SJ, Carlson GP, Holiday TA, *et al*. 1990. Hyperkalemic periodic paralysis in horses. *J Am Vet Med Assoc* 197:1009–17.
29. Glattke TJ, Runge CA. 1984. Comments on the origin of short latency auditory potentials. In *Audition in Childhood: Method of Study*, edited by Beasley DS, 81–91. San Diego: College Hill Press.
30. Chiappa KH. 1990. Brainstem auditory evoked potentials: Interpretation. In *Evoked Potentials in Clinical Medicine*, edited by Chiappa KH, 223–285. New York: Raven Press.
31. Rolf SL, Reed SM, Melnick W, *et al*. 1987. Auditory brainstem response testing in anesthetized horses. *Am J Vet Res* 48:910–14.
32. Mayhew IG, Washbourne JR. 1997. Brainstem auditory evoked potentials in horses and ponies. *Vet J* 153:107–13.
33. Bedenice D, Hoffman AM, Parrott B, *et al*. 2001. Vestibular signs associated with suspected lighting strike in two horses. *Vet Rec* 149:519–22.
34. Harland MM, Stewart AJ, Marshall AE, *et al*. 2006. Diagnosis of deafness in a horse by brainstem auditory evoked potential. *Can Vet J* 47:151–4.
35. Aminoff MJ. 1986. Electroencephalography: General principles and clinical applications. In *Electrodiagnosis in Clinical Neurology*, edited by Aminoff MJ, 21–75. New York: Churchill Livingstone.
36. Steiss JE, Cox NR, Knecht CD. 1990. Electroencephalographic and histopathologic correlations in eight dogs with intracranial mass lesions. *Am J Vet Res* 51:1286–91.
37. Klemm WR. 1989. Electroencephalography in the diagnosis of epilepsy. *Probl Vet Med* 1: 535–57.
38. Niedermeyer E, Lopes da Silva F. 2005. *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, Philadelphia: Lippincott Williams & Wilkins.
39. Redding RW. 1987. Electroencephalography. In *Veterinary Neurology*, edited by Oliver JE, Horlein BF, Mayhew IG, 111–45. Philadelphia: W.B. Saunders Co.
40. Andrews FM. 2004. Electrodiagnostic aids and selected neurologic diseases. In *Equine Internal Medicine*, edited by Reed SM, Bayly WM, Sellon DC, 546–59. St. Louis: Saunders.
41. Auer JA, Amend JF, Garner HE, *et al*. 1979. Electroencephalographic responses during volatile anesthesia in domestic ponies: A comparative study of isoflurane, enflurane, methoxyflurane, and halothane. *J Equine Med Surg* 3:130–34.
42. Dunigan CE, Oglesbee MJ, Podell M, *et al*. 1995. Seizure activity associated with equine protozoal myeloencephalitis. *Prog Vet Neurol* 6:50–4.
43. Ekström PM, Short CE, Geimer TR. 1993. Electroencephalography of detomidine-ketamine-halothane and detomidine-ketamine-isoflurane anesthetized horses during orthopedic surgery. *Vet Surg* 22:414–8.
44. Garner HE, Amend JF, Rosborough JP, *et al*. 1972. Electrodes for recording cortical electroencephalograms in ponies. *Lab Anim Sci* 22:262–5.
45. Giovagnoli G, Feo MR de, Frascarelli M, *et al*. 1996. The use of EEG and ECG ambulatory technique in horses: preliminary observations. *Pferdeheilkunde* 12:446–9.
46. Grabow JD, Anslow RO, Spalatin J. 1969. Electroencephalographic recordings with multicontact depth probes in a horse. *Am J Vet Res* 30:239–43.
47. Haga HA, Dolvik NI. 2005. Electroencephalographic and cardiovascular variables as nociceptive indicators in isoflurane-anaesthetized horses. *Vet Anaesth Analg* 32:128–35.
48. Johnson CB, Bloomfield M, Taylor PM. 1999. Effects of ketamine on the equine electroencephalogram during anesthesia with halothane in oxygen. *Vet Surg* 28:380–5.
49. Johnson CB, Bloomfield M, Taylor PM. 2000. Effects of guaiphenesin on the equine electroencephalogram during anaesthesia with halothane in oxygen. *Vet Anaesth Analg* 27:6–12.
50. Johnson CB, Bloomfield M, Taylor PM. 2000. Effects of thiopentone on the equine electroencephalogram during anaesthesia with halothane in oxygen. *Vet Anaesth Analg* 27:82–8.
51. Johnson CB, Bloomfield M, Taylor PM. 2003. Effects of midazolam and sarmazenil on the equine electroencephalogram during anaesthesia with halothane in oxygen. *J Vet Pharmacol Ther* 26:105–12.
52. Johnson CB, Taylor PM. 1998. Comparison of the effects of halothane, isoflurane and methoxyflurane on the electroencephalogram of the horse. *Br J Anaesth* 81:748–53.
53. Johnson CB, Young SS, Taylor PM. 1994. Analysis of the frequency spectrum of the equine electroencephalogram during halothane anaesthesia. *Res Vet Sci* 56:373–8.
54. Lacombe VA, Podell M, Furr M, *et al*. 2001. Diagnostic validity of electroencephalography in equine intracranial disorders. *J Vet Intern Med* 15:385–93.
55. Lapras M, Florio R, Joubert L, *et al*. 1968. Normal electroencephalogram in the horse. Its pathological variations in West Nile viral

meningoencephalomyelitis. Relations to clinical findings, virology and histopathology. *Revue Méd vét* 119: 673–93.
56. Lewin W, Tînhardt H. 1998. Non-invasive EEG of the conscious standing horse. *Pferdeheilkunde* 14:285–94.
57. Murrell JC, Johnson CB, White KL, *et al*. 2003. Changes in the EEG during castration in horses and ponies anaesthetized with halothane. *Vet Anaesth Analg* 30:138–46.
58. Murrell JC, White KL, Johnson, *et al*. 2005. Investigation of the EEG effects of intravenous lidocaine during halothane anaesthesia in ponies. *Vet Anaesth Analg* 32:212–21.
59. Mysinger PW, Redding RW, Vaughan JT, *et al*. 1985. Electroencephalographic patterns of clinically normal, sedated, and tranquilized newborn foals and adult horses. *Am J Vet Res* 46:36–41.
60. Otto KA, Voigt S, Piepenbrock S, *et al*. 1996. Differences in quantitated electroencephalographic variables during surgical stimulation of horses anesthetized with isoflurane. *Vet Surg* 25:249–55.
61. Stromberg MW, Kitchell RL, Unsenik FA, *et al*. 1962. Electrocorticographic patterns in normal burros and pigs. *Am J Vet Res* 23:737–43.
62. Usenick MW, Kitchell RL, Herschler RG, *et al*. 1962. A surgical technique for permanent implantation of electrocorticographic electrodes in the burro and pigs. *Am J Vet Res* 23:70–3.
63. Williams DC, Holliday TA, Aleman MR. 2002. Sleep in the horse: An electroencephalographic study. *Proc 20th Annu Meeting ACVIM* 20:335.
64. Ruckebusch Y. 1970. Loss of consciousness during sleep in the horse and cow. *Cah Mèd Vet* 39:210–25.
65. Ruckebush Y, Barbey P, Guillemot P. 1970. Les états de sommeil chez le cheval. *C R Séances Soc Biol* 164:638–65.
66. Ruckebush Y, Gaujoux M, Eghbali B. 1977. Sleep cycles and kinesis in the foetal lamb. *Electroencephalogr Clin Neurophysiol* 42: 226–37.
67. Ruckebush Y. 1972. Development of sleep and wakefulness in the foetal lamb. *Electroencephalogr Clin Neurophysiol* 32:119–28.
68. Ruckebush Y. 1972. The relevance of drowsiness in the circadian cycle of farm animals. *Anim Behav* 20:637–43.
69. Ruckebush Y. 1974. Sleep deprivation in cattle. *Brain Res* 78:495–9.
70. Croft PG. 1964. The EEG as an aid to diagnoses of nervous diseases in the dog and cat. *J Small Anim Pract* 5:540–1.
71. Redding RW. 1964. A simple technique for obtaining an electroencephalogram of the dog. *Am J Vet Res* 25:854–7.
72. Klemm WR. 1965. Technical aspects of electroencephalography in animal research. *Am J Vet Res* 26:1237–48.
73. Klemm WR, Hall CL. 1974. Current status and trends in veterinary encephalography. *J Am Vet Med Assoc* 164:529.
74. Usenick MW, Kitchell RL, Herschler RG, *et al*. 1962. The EEG as an aid to diagnosis of nervous diseases in the dog and cat. *J Small Anim Pract* 3:205–8.
75. Holliday TA, Cunningham JG, Gutnick MJ. 1970. Comparative clinical and electroencephalographic studies of canine epilepsy. *Epilepsia* 11:281–92.
76. Berendt M, Høgoenhaven H, Flagstad A, *et al*. 1999. Electroencephalography in dogs with epilepsy: Similarities between human and canine findings. *Acta Neurol Scand* 99:276–83.
77. Jaggy A, Bernardini M. 1998. Idiopathic epilepsy in 125 dogs: A long-term study. Clinical and electroencephalographic findings. *J Small Anim Pract* 39:23–9.
78. Steiss JE. 2003. Electrodiagnostic evaluation. In *Clinical Neurology in Small Animals. Localization, Diagnosis and Treatment*, edited by Braund KG. Ithaca, New York: International Veterinary Information Service.
79. Viitmaa R, Cizinauskas S, Bergamasco LA, *et al*. 2006. Magnetic resonance imaging findings in Finnish Spitz dogs with focal epilepsy. *J Vet Intern Med* 20:305–10.
80. Otto KA, Mally P. 2003. Noxious stimulation during orthopaedic surgery results in EEG 'arousal' or 'paradoxical arousal' reaction in isoflurane-anaesthetised sheep. *Res Vet Sci* 75:103–12.
81. Otto K, Short CE. 1991. Electroencephalographic power spectrum analysis as a monitor of anesthetic depth in horses. *Vet Surg* 20: 362–71.
82. Haga HA, Dolvik NI. 2002. Evaluation of the bispectral index as an indicator of degree of central nervous system depression in isoflurane-anesthetized horses. *Am J Vet Res* 63:438–42.
83. Purohit RC, Mysinger PW, Redding RW. 1981. Effects of xylazine and ketamine hydrochloride on the electroencephalogram and the electrocardiogram in the horse. *Am J Vet Res* 42:615–19.
84. Hepburn RJ, Furr MO. 2004. Sinonasal adenocarcinoma causing central nervous system disease in a horse. *J Vet Intern Med* 18:125–31.

85. Heath SE, Artsob H, Bell RJ, *et al*. 1989. Equine encephalitis caused by snowshoe hare (California serogroup) virus. *Can Vet J* 30:669–71.
86. Lunn DP, Cuddon PA, Shaftoe S, *et al*. 1991. Familial occurrence of narcolepsy in Miniature horses. *Equine Vet J* 25:483–7.
87. Knecht CD, Sorjonen DC, Simpson ST. 1984. Ancillary tests in the diagnosis of seizures. *J Anim Hosp Assoc* 20:455.
88. Speckmann EJ, Elger CE. 2005. Introduction to neurophysiological basis of the EEG and DC potentials. In *Electroencephalography*, edited by Niedermeyer E., Lopes Da Silva F, 17–30. Philadelphia: Lippincott Williams & Wilkins.
89. Sharbrough FW. 1990. Electrical fields and recording techniques. In *Current Practice of Clinical Electroencephalography*, edited by Daly DD, Pedley TA, 29–49. New York: Raven Press.
90. Holliday TA, Williams DC. 1999. Clinical electroencephalography in dogs. *Vet Neurol Neurosurg*. www.neurovet.org
91. Engel J, Pedeley TA. 1998. *Epilpesy*. Philadelphia: Lippincott-Raven.
92. March PA, Muir WW. 2005. Bispectral analysis of the electroencephalogram: a review of its development and use in anesthesia. *Vet Anaesth Analg* 32:241–55.
93. Miller SM, Short CE, Ekström PM. 1995. Quantitative electroencephalographic evaluation to determine the quantity of analgesia during anesthesia of horses for arthroscopic surgery. *Am J Vet Res* 56:374–9.
94. MacLean AW, Lue F, Moldofksy H. 1995. The reliability of visual scoring of alpha EEG activity during sleep. *Sleep* 18:565–9.
95. Houpt KA. 1980. The characteristics of equine sleep. *Equine Pract* 2–4:8–17.
96. Itabisashi T, Horino R, Hirano K, *et al*. 1990. Electroencephalographic observation on sheep and cattle with experimental cerebrocortical necrosis. *Jpn J Vet Sci* 52:551–8.
97. Suzuki M, Sitizyo K, Takeuchi T, *et al*. 1990. Electroencephalogram of Japanese black calves affected with cerebrocortical necrosis. *Jpn J Vet Sci* 52:1077–87.
98. Suzuki M, Sitizyo K, Takeuchi T, *et al*. 1990. Electroencephalograms of three Japanese Black calves with hydranencephaly. *J Jpn Vet Med Assoc* 43:723–7.
99. DeLahunta A, Cummings JF. 1965. The clinical and electroencephalographic features of hydrocephalus in three dogs. *J Am Vet Med Assoc* 146:954.
100. Holliday TA, Williams DC. 1998. Interictal paroxysmal discharges in the electroencephalograms of epileptic dogs. *Clin Tech Small Anim Pract* 13:132–43.
101. Aleman M, Brosnan RJ, Williams DC, *et al*. 2005. Malignant hyperthermia in a horse anesthetized with halothane. *J Vet Intern Med* 19:363–6.

11
Anesthetic Considerations for Horses with Neurologic Disease

Alison Smith

Neurologic disease can present a variety of challenges for the anesthetist. The unique anatomical features of the brain limit its ability to respond to inflammatory, traumatic, and neoplastic challenges. Horses presenting with spinal cord or peripheral neuropathies can be challenging to the anesthetist due to the increased danger of a large, ataxic patient. The goal of neurologic anesthesia is to maintain adequate nourishment and blood delivery to the brain, minimize the development of seizures, minimize the effects of ataxia on the patient's safety, and prevent further deterioration of neurologic status.

An understanding of the anatomy and physiology of the nervous system and how it relates to anesthesia is important in understanding how best to maximize patient safety and minimize morbidity and mortality.

The brain is housed entirely within a bony cavity. This rigid structure does not allow for an increase in volume when faced with a traumatic, inflammatory, or neoplastic insult. Minor changes in cerebral blood flow (CBF), cerebrospinal fluid (CSF), or tissue volume (i.e., mass) can quickly result in a moderate-to-severe increase in intracranial pressure (ICP). Elevated ICP can cause regional and global cerebral ischemia and hypoxia due to a reduction in cerebral perfusion pressure (CPP) and CBF, and ultimately can lead to potentially fatal displacement of brain and neuronal tissue, including brainstem herniation.[1] CBF is directly proportional to CPP and indirectly proportional to cerebral vascular resistance (CVR). Of these components, only CBF can be easily influenced by the anesthetist and thus is of particular interest.

In a normal horse, CBF is under metabolic (chemical), myogenic (autoregulation), and neurogenic factors.[2] This control ensures consistent, high flow of blood to the brain over a range of arterial blood pressures. The mean arterial pressure (MAP) range within which CBF remains under autoregulatory control has not been defined in horses; however, in humans, the CBF remains consistent over 70–140 mm Hg, and animals may have better regulation of flow at lower arterial pressures.[2] Horses, due to their large size, undergo large orthostatic shifts when positioned in lateral or dorsal recumbency for general anesthesia.[3] These fluid shifts can alter MAP and thus have an effect on CPP.

Chemical or metabolic factors that influence CBF include cerebral metabolic rate (CMR), the partial pressure of arterial carbon dioxide (P_aCO_2), the partial pressure of arterial oxygen (P_aO_2), and temperature. An increase in CMR will lead to an increase in CBF.[2] Anesthetics, both injectable and inhaled, can alter CMR and therefore influence CBF. Likewise, an increase in the temperature of the brain causes an increase in CBF.

There is a directly proportionate relationship between CBF and P_aCO_2. These changes are due to intra- and extracellular pH alterations. Hypocapnia and alkalemia lead to a decrease in CBF due to vasoconstriction, resulting in an increase in CVR. Conversely, hypercapnia and acidemia result in an increase in CBF, due to vasodilation.[4] Hypoxemia, that is, P_aO_2 less than 60 mm Hg, causes an increase in CBF, resulting from vasodilation. Hyperoxia may mildly decrease CBF.[2]

Brosnan and colleagues directly measured the ICP of awake horses and horses undergoing isoflurane anesthesia. A transducer was surgically implanted at the level of the subarachnoid space. Measurements of awake, standing horses revealed ICP values in the range of 2 ± 4 mm Hg, which are consistent with other animals.[5] In contrast, anesthesia and recumbency affects the body's ability to maintain normal CBF, CPP, and ICP. When horses are placed in head-dependent positions, both ICP and CPP increase 10-fold over values in awake, standing horses.[6] The clinical significance of this observation is unclear. A marked increase in ICP and CPP in normal, anesthetized, recumbent horses suggests that horses with preexisting elevations of ICP and CPP may be at a greater risk for catastrophic brain herniation. Additionally, normal horses may experience mild-to-marked cerebral hypoxia and ischemia whilst receiving general anesthesia.

Premedication of neurologic patients is generally recommended and can be quite helpful in maximizing the safety of the anesthetic event. Since premedicants help to decrease anxiety, provide smoother induction, maintenance, and recovery phases of anesthesia, decrease the required doses of both induction and maintenance drugs required for anesthesia, and can provide analgesia to the patient, they should generally be included in an anesthetic protocol. Exceptions to this may include severely obtunded patients in whom further central nervous system (CNS) depression is not desirable.

Alpha-2 agonists are commonly used for sedation of horses with neurologic disease. Examples of commonly used alpha-2 agonists include xylazine, detomidine, medetomidine, and romifidine. Advantages to the use of this class of sedatives include good-to-profound sedation that is fairly reliable, muscle relaxation, and analgesia, although the duration of analgesia is generally shorter than the sedative effects. These drugs can be administered both intravenously and intramuscularly. This class of drugs can also cause hypotension, respiratory depression, decreased cardiac output, and bradycardia.[7–9]

Some controversy exists regarding the use of acepromazine, a phenothiazine tranquilizer, in animals with neurologic disease, and especially in patients with a history of seizures or undergoing a procedure that can potentially induce seizures. The belief is that acepromazine lowers the seizure threshold and therefore could potentiate seizures. In a small study in dogs with a history of seizures, which were administered acepromazine, there was no increase in seizure activity.[10] Administration of acepromazine results in mild tranquilization and anxiolysis. Johnson et al., in the Confidential Enquiry of Perioperative Equine Fatalities, demonstrated that premedication with acepromazine is related to increased survival.[11] It can also cause mild-to-profound systemic vasodilation, resulting in hypotension, although in normovolemic patients, this may not be clinically significant.[12] The duration of action is longer than other sedatives and tranquilizers that are commonly administered. Acepromazine should be avoided in shocky, dehydrated, or hypovolemic patients, or in patients undergoing procedures that may result in excessive hemorrhage. The decision to use acepromazine in the neurologic patient should be based on the individual patient. Horses that are especially nervous and difficult to sedate using alpha-2 agonists may benefit from the inclusion of acepromazine in the sedation protocol.

The benzodiazepine class of tranquilizers can also be used as part of the preanesthetic protocol in horses with neurologic disease. Both diazepam and midazolam may be appropriate. These drugs are especially beneficial in patients that are exhibiting seizures, as they have anticonvulsant capabilities. The benzodiazepine class of drugs functions by increasing the activity of gamma-aminobutyric acid (GABA), and thus causes depression of the central nervous system.[13] The benzodiazepines also decrease CBF.[14] Diazepam and midazolam can also provide muscle relaxation, and mild tranquilization, especially at higher doses.[15] These last two effects are important considerations, as an excited horse may not become sedate enough for induction and yet may become profoundly ataxic, especially if ataxia is a component of the horse's presenting clinical signs. This ataxia may further excite the horse, precluding a safe and controlled induction to general anesthesia. In an already ataxic horse, benzodiazepines should not be the first choice drug for sedation, but can be safely used as an adjunct for the induction of general anesthesia, or to control seizures.

Opioid analgesics can be included in the premedication protocol. Butorphanol is commonly administered to horses as a premedicant. As a mu antagonist–kappa agonist opioid, butorphanol provides minor sedation and analgesia with few side

effects. When given concurrently with an alpha-2 agonist or phenothiazine tranquilizer, the sedative and analgesic effects of both drugs are synergistically enhanced. This effect can be beneficial for a neurologic patient. Side effects of butorphanol are usually mild and can include respiratory depression, decreased heart rate, and ataxia. Butorphanol is much less likely to cause increased locomotion compared with morphine or other pure mu opioid agonists.[16]

Other opioids can likewise be administered to horses as part of a premedication protocol. These can include pure mu agonist opioids like morphine and fentanyl, or a partial mu agonists like buprenorphine. Morphine and fentanyl provide potent analgesia, but their sedative effects can vary in horses. Horses may exhibit mild-to-profound sedation, but excitation and increased locomotion can also occur.[17] Morphine remains an option for providing analgesia to horses undergoing potentially painful procedures[18]; however, the degree of analgesia can vary from profound to none, and increased excitation may occur.

Barbiturates are most frequently used for induction of anesthesia in patients with neurologic disease. Barbiturates decrease CMR and ICP and are neuroprotective via prevention of free radical formation, enhancement of GABA activity, and inhibition of calcium ion influx.[19,20] Thiopental is the induction drug of choice in horses with suspected or confirmed traumatic brain injury. Side effects of thiopental administration include hypotension and prolonged, disordered recoveries, even in neurologically normal patients.[21,22] An ataxic horse that receives thiopental may have a rough recovery with multiple unsuccessful, uncoordinated attempts to stand; however, the beneficial cerebral effects make thiopental an excellent choice for patients with central neurologic disease.

Propofol is commonly used alone and combined with thiopental for induction of humans and dogs undergoing anesthesia for neurologic disease.[20] Horses have a variable response to propofol, ranging from mild sedation to induction of general anesthesia. The degree of anesthesia achieved is dose dependent and is improved with premedication.[23,24] The cost associated with the larger dose required for more reliable anesthesia may preclude routine use of propofol in clinical practice.

Human neuroanesthesia has embraced the use of propofol infusions for total intravenous anesthesia in patients at higher risk for elevated ICP as propofol is better at reducing ICP than is inhalant anesthesia.[25] Propofol is generally inadequate for total intravenous anesthesia as a sole agent and is generally combined with either an alpha-2 agonist or ketamine. Recovery from propofol anesthesia is generally excellent, although hypoxemia and hypercapnia may occur.[23,26]

Use of ketamine in horses with suspected or confirmed traumatic brain injury should be undertaken cautiously. Ketamine, as a dissociative anesthetic, raises CMR, increases CBF and ICP, and can cause seizure-like activity on an electroencephalogram.[14,27] Ketamine may be a viable choice for induction in patients with peripheral neurologic disease and in whom seizures and an increase in ICP are unlikely. Ketamine should not be used alone, as the potential for seizures and excessive muscle rigidity may result. The negative CNS effects can be attenuated with concomitant administration of a benzodiazepine.[14] Muscle relaxation can also be provided by an alpha-2 agonist or guaifenesin.

Inhalants are recommended for maintenance of anesthesia in horses. Halothane, isoflurane, and sevoflurane can all be used successfully in patients with neurologic disease. The inhalants allow more precise control of depth of anesthesia and allow for rapid recovery from anesthesia. The inhalants can cause a reduction in CPP due to vasodilation-induced reduction in MAP.[28,29] There is a risk that use of an inhalant can increase CBF. Much of this increase is the result of an increase in P_aCO_2. All of the inhalants, especially isoflurane, are respiratory depressants, and hypoventilation and hypercapnia may result.[30] This could lead to an increase in ICP.[31] Intermittent positive pressure ventilation can reduce or prevent hypoventilation.

Hypocapnic hyperventilation has long been a cornerstone of therapy in patients with suspected or confirmed increase in ICP.[4,32] Although a method of direct measurement of ICP in horses is possible, it is not feasible in most clinical patients.[5] Elevated ICP can be indirectly inferred from MAP: in order to maintain CPP, MAP will increase in response to increased ICP. This phenomenon is the Cushing's effect.[2] Hypercapnic, spontaneously ventilated horses anesthetized with isoflurane have elevated ICP when compared to normocapnic horses receiving controlled ventilation.[3] The goal of hyperventilation therapy is to maintain P_aCO_2 between 30 and 40 mm Hg.

Excessive hypocapnia (<25 mm Hg) reduces CBF excessively and should be avoided. Hypoxemia should likewise be avoided. Providing an enriched oxygen supply, and maintaining the horse on mechanical ventilation, should be utilized as necessary to maintain P_aO_2 greater than 80 mm Hg.

An elevated ICP that cannot be managed by hyperventilation alone may benefit from hyperosmotic solutions. Mannitol is frequently used to decrease cerebral volume by drawing fluid out of neuronal tissue. Hypertonic saline can also be administered for this purpose.[1]

Hypotension should be avoided in the healthy horse, and the neurologic horse is no exception. As CPP is a function of MAP, ensuring adequate systemic blood pressures will help to ensure that cerebral perfusion is maintained. The diseased brain may lose its ability to autoregulate, so cerebral perfusion becomes flow dependent. Fluids should be administered in order to help maintain MAP and CPP. Any balanced salt electrolyte solution is acceptable; these fluids should not contain glucose or glucose precursors, including lactate. Hypergylcemia is associated with increased morbidity.[20] Inotropic support, including dobutamine and ephedrine, should be used as needed to maintain acceptable MAP.[33]

Monitoring a neurologic horse under general anesthesia is similar to monitoring a healthy horse anesthetized with an inhalant. Direct arterial blood pressure should be monitored, as blood pressure can change very quickly, and maintaining adequate MAP is essential in limiting morbidity.[34] An end-tidal CO_2 ($EtCO_2$) monitor is helpful to noninvasively gauge ventilation trends.[35] However, the difference between $EtCO_2$ and $PaCO_2$ can be large, so an arterial blood gas should be evaluated to ensure that the hyperventilated horse is in fact hypocapnic.[36] An arterial blood gas will also ensure that the patient is not hypoxemic. An electrocardiogram should also be utilized to ensure that the horse does not have any cardiac arrhythmias that would interfere with maintenance of CBF. Although not essential, a pulse oximeter to measure oxygen saturation can provide additional information about the stability of the patient.

Recovery from anesthesia can be dangerous with normal horses; horses suffering from neurologic disease are often ataxic which can increase the difficulty of recovery. Brosnan et al. speculates that some of the difficult and delayed recoveries from anesthesia may in fact be due to increased ICP and its sequelae, and horses with preexisting neurologic conditions are certainly susceptible.[6] Horses should be placed in a recovery area that is free of obstructions and preferably well padded. Oxygen should be supplemented via an endotracheal tube, nasotracheal tube, or nasopharyngeal tube to ensure adequate oxygenation during the recovery period. Horses that had myelography and received contrast solution can be placed with their head elevated, to encourage the contrast solution to drain away from the brain. When elevating the head, be sure to use objects that will not injure the horse nor be in the way during recovery. Assistance, in the form of head and or tail ropes, and physical restraint by trained personnel, can also increase the safety of recovery for the horse. If a horse has a cervical injury or underwent cervical surgery, the use of a head rope may cause more harm than good, however. In these situations, a tail rope alone may provide enough assistance without further risking trauma to the horse's neck. The recovery stall should be as quiet as possible, so as to not disturb the horse. Diazepam or midazolam should be available during the recovery phase in the event of seizures. Additional sedation—frequently a lower dose of the sedative used for premedication—can also be given to the horse to smooth the recovery period.

NEUROLOGIC COMPLICATIONS OF GENERAL ANESTHESIA

Neurologic complications can result in patients that have preexisting neurologic complications or in horses anesthetized for other reasons. Peripheral neuropathies can result from improper positioning of the horse. These neuropathies can include trauma to the radial and peroneal nerves, and less commonly the femoral nerve. Femoral nerve injury occurs from caudal extension of the limb, stretching the femoral nerve as it passes over the psoas muscle. Horses should be positioned on thickly padded tables devoid of pressure points. All limbs should be independently supported and in a neutral position. When the horse is in lateral recumbency, the dependent thoracic limb should be pulled forward to relieve pressure from the radial nerve. Postanesthetic neuropathy may closely

resemble postanesthetic myopathy. Treatment for both is largely supportive and includes intravenous fluids, physical support of the horse, analgesics, and sedatives.

Postanesthetic cerebral necrosis is a rare complication associated with general anesthesia in horses. Clinical signs can occur minutes to hours after anesthesia and include bilateral blindness with normal pupillary light reflex, abnormal behaviors including pacing and head pressing, lethargy, and seizures. In a case report of five horses that were euthanized following the development of postanesthetic cerebral necrosis, McKay et al. reported that these horses' brains displayed neuronal necrosis consistent with cerebral ischemia.[37] Thus, any horse that undergoes a period of hypoperfusion and/or hypoxemia is at risk for the development of postanesthetic cerebral necrosis. Horses that are anesthetized for colic may be at increased risk of developing cerebral ischemia, as they often have circulatory compromise. Ensuring proper blood pressure and oxygenation should minimize the risk of this complication.

Postanesthetic myelomacia is another uncommon complication of general anesthesia in horses. Horses will be unable to stand in recovery, have an inability to use their hind limbs and loss of deep pain perception. This condition generally affects young horses in dorsal recumbency that have undergone a short duration of anesthesia.[38] The mechanism of action for the development of myelomacia is not known but is hypothesized to be related to ischemia and hypoxia of the spinal cord.[39] This may be very difficult to distinguish from femoral paralysis.

ANESTHESIA FOR MYELOGRAPHY

Horses requiring general anesthesia for myelography likely constitute the bulk of neurologic anesthetic cases. There are three components that contribute to the challenge facing the anesthetist: (1) injection of a volume of fluid into the CSF which could alter cerebral fluid balance; (2) introduction of a potentially noxious substance into the CSF; and (3) the patient's preexisting neurologic status. Injection of contrast solution into the CSF can change the volume of fluid housed within the cranial vault and lead to an increase in ICP. Frequently, a volume of CSF is removed from the horse before injection of contrast media. While this practice decreases the chance for elevated ICP, the fluid balance within the brain may be temporarily altered. The choice of contrast solution can influence the risk of complications. Iohexol cervical myelography had fewer complications than metrizamide in a clinical study. Side effects included seizures, prolongation of anesthetic recovery, and worsening of the horse's presenting neurologic signs.[40] The horse's neurologic status must also be taken into consideration. Many horses requiring myelography are ataxic and thus pose a challenge for safe recovery from anesthesia.

ANESTHESIA FOR CERVICAL SURGERY

Cervical vertebral surgery can present a few challenges to the anesthetist. These patients are generally ataxic both pre- and postsurgery. Analgesia is an important consideration for these cases, as the procedures can be quite painful. Recovery is also a very critical time for these patients, as it is easy for them to traumatize their neck as they emerge from anesthesia and attempt to stand. The use of a head rope can be both a help and a hindrance. Guidance of the head may allow the horse to stand with minimal scrambling, but it can also place undue torque and strain on the neck and worsen the cervical trauma. Only very careful use of a head rope by an experienced individual should be allowed. Sedation in recovery, generally with alpha-2 agonists, can limit the development of emergence delirium.

ANESTHESIA FOR HEAD TRAUMA OR CRANIAL MASS

The main goal in a patient with head trauma or a cranial mass is to prevent an increase in ICP and to keep the CMR low. Minimal sedation may be needed, as these patients can be quite obtunded prior to anesthesia. If additional sedation is required, alpha-2 agonists are appropriate. If the horse is recumbent, benzodiazepines may also be administered. Thiopental should be used for the induction of general anesthesia, and the horse maintained on an inhalant. IPPV is essential to keep the $PaCO_2$ low enough to decrease CBF, and therefore limit any increase in ICP. IPPV, by use of a demand vale, should likewise be continued during recovery, until the horse is conscious enough to maintain appropriate ventilation. Recovery may be prolonged, and a patient recumbent prior to anesthesia may remain recumbent postanesthesia.

Table 11.1. Key Points of Neurologic Anesthesia

Physiology	Elevated ICP can lead to cerebral ischemia and hypoxia
	ICP influenced by MAP, CBF
	CBF proportional to P_aCO_2
	ICP may be elevated in normal, anesthetized horses
Anesthetic drugs	Alpha-2 agonists most commonly used for sedation
	ACP may potentiate seizures
	BZD are anticonvulsants, may exacerbate ataxia
	Thiopental is neuroprotective, first choice for induction of anesthesia
	Propofol is neuro-friendly, but anesthetic effects are unpredictable
	Ketamine increases CBF and ICP and can potentiate seizures
	Inhalants recommended for maintenance of anesthesia
Maintenance	IPPV with mild hypocapnia
	Hyperosmolar solutions can help decrease ICP
	MAP measured and maintained >70 mm Hg
	Glucose- and lactate-free IV fluids
	Arterial blood gases
Recovery	Supplemental oxygen
	Assisted recovery, head and tail ropes
	Area free from distractions

ACP, acepromazine; BZD, benzodiazepine; CBF, cerebral blood flow; ICP, intracranial pressure; IPPV, intermittent positive pressure ventilation; IV, intravenous; MAP, mean arterial pressure.

CONCLUSIONS

Providing safe anesthesia for a patient with neurologic disease does not differ greatly from the protocol for a healthy horse. Regardless of the patient's status, careful monitoring and early recognition and treatment of abnormalities and complications will decrease the incidence of morbidity and mortality (Table 11.1).

REFERENCES

1. Mayer S, Chong J. 2002. Critical care management of intracranial pressure. *J Intensive Care Med* 17:55–67.
2. Drummond J, Patel P. 2000. Cerebral physiology and the effects of anesthetics and techniques. In *Anesthesia*, edited by Miller R, 695–733. Philadelphia: Churchill Livingstone.
3. Brosnan RJ, Steffey EP, *et al*. 2003. Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses. *Am J Vet Res* 64:21–5.
4. Raichle M, Plum F. 1972. Hyperventilation and cerebral blood flow. *Stroke* 3:566–75.
5. Brosnan RJ, LeCouteur RA, *et al*. 2002. Direct measurement of intracranial pressure in adult horses. *Am J Vet Res* 63:1252–6.
6. Brosnan RJ, Steffey EP, *et al*. 2002. Effects of body position on intracranial and cerebral perfusion pressures in isoflurane-anesthetized horses. *J Appl Physiol* 92:2542–6.
7. Bueno A, Cornick-Seahorn J, *et al*. 1999. Cardiopulmonary and sedative effects of intravenous administration of low doses of medetomidine and xylazine to adult horses. *Am J Vet Res* 60:1371–6.
8. Taylor P, Bennett R, *et al*. 2001. Comparison of detomidine and romifidine as premedicants before ketamine and halothane anesthesia in horses undergoing elective surgery. *Am J Vet Res* 62:359–63.
9. Yamashita K, Muir W, *et al*. 2002. Clinical comparison of xylazine and medetomidine for premedication of horses. *J Am Vet Med Assoc* 221:1144–9.
10. Garner J, Kirby R, *et al*. 2004. The use of acepromazine in dogs with a history of seizures. *J Vet Emerg Crit Care Soc* 14:S1–17.
11. Johnston G, Eastment J, *et al*. 2002. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. *Vet Anaesth Analg* 29:159–70.
12. Murison P, Clutton R, *et al*. 2003. Blood pressure and electrocardiographic effects of acepromazine in anesthetized horses. *Vet Anaesth Analg* 30:94–5.
13. Plumb D. 2002. *Veterinary Drug Handbook*. Ames, Iowa State Press.

14. Reves J, Glass P, *et al*. 2000. Nonbarbiturate intravenous anesthetics. In *Anesthesia*, edited by Miller R, 228–272. Philadelphia: Churchill Livingstone.
15. Muir W, Sams R, *et al*. 1982. Pharmacodynamic and pharmacokinetic properties of diazepam in horses. *Am J Vet Res* 43:1756–62.
16. Sellon D, Monroe V, *et al*. 2001. Pharmacokinetics and adverse effects of butorphanol administered by single intravenous injection or continuous intravenous infusion in horses. *Am J Vet Res* 62:183–9.
17. Bennett R, Steffey E. 2002. Use of opioids for pain and anesthetic management in horses. *Vet Clin North Am Equine Prac* 18(1):47–60.
18. Mirica E, Clutton R, *et al*. 2003. Problems associated with perioperative morphine in horses: a retrospective case analysis. *Vet Anaesth Analg* 30: 147–55.
19. Fragen R, Avram M. 2000. Barbiturates. In *Anesthesia*, edited by Miller R, 209–27. Philadelphia: Churchill Livingstone.
20. Hirsch N. 2003. State of the art: advances in neuroanaesthesia. *Anaesthesia* 58:1162–5.
21. Hubbell J, Hinchcliff K, *et al*. 2000. Anesthetic, cardiorespiratory, and metabolic effects of four intravenous regimens induced in horses immediately after maximal exercise. *Am J Vet Res* 61: 1545–52.
22. Wagner A, Mama K, *et al*. 2002. Behavioral responses following eight anesthetic induction protocols in horses. *Vet Anaesth Analg* 29:207–11.
23. Mama K, Steffey EP, *et al*. 1995. Evaluation of propofol as a general anesthetic for horses. *Vet Surg* 24:188–94.
24. Frias A, Marsico F, *et al*. 2003. Evaluation of different doses of propofol in xylazine premedicated horses. *Vet Anaesth Analg* 30:193–201.
25. Peterson K, Landsfeldt U, *et al*. 2002. ICP is lower during propofol anaesthesia compared to isoflurane and sevoflurane. *Acta Neurochir Suppl* 81: 89–91.
26. Bettschart-Wolfensberger R, Freeman S, *et al*. 2001. Infusion of a combination of propofol and medetomidine for long-term anesthesia in ponies. *Am J Vet Res* 62:500–7.
27. Albanese J, Arnaud S, *et al*. 1997. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology* 87:1328–34.
28. Bundgaard H, von Oettingen G, *et al*. 1998. Effects of sevoflurane on intracranial pressure, cerebral blood flow and cerebral metabolism. A dose– response study in patients subjected to craniotomy for cerebral tumours. *Acta Anaesth Scand* 42: 621–7.
29. Sponhein S, Skraastad O, *et al*. 2003. Effects of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on intracranial and cerebral perfusion pressures in children. *Acta Anaesth Scand* 47:932–38.
30. Grosenbaugh D, Muir W. 1998. Cardiorespiratory effects of sevoflurane, isoflurane, and halothane anesthesia in horses. *Am J Vet Res* 59:101–6.
31. Cold GE, Bundgaard H, *et al*. 1998. ICP during anaesthesia with sevoflurane: a dose-response study. Effect of hypocapnia. *Acta Neurochir Suppl* 71: 279–81.
32. Stocchetti N, Maas AI, *et al*. 2005. Hyperventilation in head injury: a review. *Chest* 127:1812–27.
33. Moppett I, Wild M, *et al*. 1992. Effects of ephedrine, dobutamine and dopexamine on cerebral haemodynamics: transcranial Doppler studies in healthy volunteers. *Br J Anaesth* 92:39–44.
34. Duke T, Filzek U, *et al*. 2006. Clinical observations surrounding an increased incidence of postanesthetic myopathy in halothane-anesthetized horses. *Vet Anaesth Analg* 33:122–7.
35. Palmer J. 2005. Ventilatory support of the critically ill foal. *Vet Clin North Am Equine Pract* 21(2): 457–86.
36. Teixeira Neto F, Luna S, *et al*. 2000. The effect of changing the mode of ventilation on the arterial-to-end-tidal CO_2 difference and physiological dead space in laterally and dorsally recumbent horses during halothane anesthesia. *Vet Surg* 29:200–5.
37. McKay JS, Forest TW, Senior M, *et al*. 2002. Postanaesthetic cerebral necrosis in five horses. *Vet Rec* 150:70–4.
38. Trim CM. 1997. Postanesthetic hemorrhagic myelopathy or myelomalacia. *Vet Clin North Am Equine Pract* 13:73–7.
39. Zink MC. 1985. Postanesthetic poliomyelomalacia in a horse. *Can Vet J* 26:275–7.
40. Widmer W, Blevins W, *et al*. 1998. A prospective clinical trial comparing metrizamide and iohexol for equine myelography. *Vet Rad Ultra* 39:106–9.
41. Matthews N, Hartke S, *et al*. 2003. An evaluation of pulse oximeters in dogs, cats and horses. *Vet Anaesth Analg* 30:3–14.

12
The Basics of Equine Neuropathology

John L. Robertson

The most important issue for veterinarians when seeing a horse with neurologic signs is determining the site of disease. Often, the veterinarian must determine whether the disease is primarily localized in the central nervous system and peripheral nerves, or whether it is a non-neurologic disease simply presenting as neurologic disease. This determination, which is sometimes difficult, will be based on the analysis of history, physical examination findings, neurologic evaluation, and laboratory tests. Arriving at an accurate diagnosis of neurologic disease is the subject of other chapters found in this book and in other reference texts.[1] This chapter focuses on procedures for dealing with pathologic evaluation of horses with suspected neurologic disease.

COMMON PRESENTATIONS AND PROBLEMS

Common presentations confronting the veterinary practitioner and pathologist in horses with suspected neurologic diseases are:

- Horses with primary musculoskeletal problems and injuries, in which there is clearly some degree of neurologic dysfunction (alterations in coordination and gait and abnormal neurologic examination), and in which there may be secondary neurologic lesions (the neurodegeneration associated with suprascapular nerve paralysis [sweeny], for example)[2]
- Horses of any age (the young and old alike) in which there is altered mentation and coordination
- Horses in which there are vague or nonspecific neurologic signs, suggestive of primary neurologic disease, but for which there can be many causes (toxic, traumatic, metabolic, neoplastic, and infectious)
- Horses with signs characteristic of a specific type of neurologic disease (e.g., the hirsuitism associated with hyperplastic or neoplastic pituitary disease)
- Horses suspected of having a neurologic disease that may be infectious in nature, and for which there is a valid concern for the health of other horses, animals, and people (many of the viral encephalitides are in this category)

Horses that appear healthy but which die unexpectedly or which are found dead present unique problems for both the practitioner and pathologist. The postmortem examination of these horses may not clearly determine a cause of death, and neurologic and cardiovascular diseases are frequently considered as part of the differential diagnosis that must be pursued.

POSTMORTEM EVALUATION OF THE NERVOUS SYSTEM OF HORSES

The most important point in this chapter can be made by stating the obvious: if the nervous system is not examined grossly and microscopically, it is impossible to find lesions and to determine their importance in the death of horses. By far, the most common error made by practitioners and by pathologists who examine dead horses is a failure to actually examine the brain, spinal cord, and peripheral nerves and to collect tissues for microscopic evaluation. There are many excuses given for avoiding a postmortem evaluation of the nervous system including

the belief that special equipment, techniques, or fixatives are required; none of these are valid reasons for not doing a neurologic postmortem.

While it is true that horses are large animals and it is physically demanding to deal with their carcasses and tissues, most veterinarians are quite capable of doing so, especially if they seek some assistance (which does not have to be skilled). Virtually all postmortem examinations, including the central nervous system, can be performed with common tools available at most hardware stores. Veterinarians in equine specialty practices or mixed practices would do well to invest roughly $100 in equipment and keep it for postmortems.

Following a systematic approach to dissection allows all practitioners to adequately sample tissues in the nervous system; one does not have to be an expert. The very first step in arriving at a definitive diagnosis is tissue collection and preservation. Once this is done, tissues can be transferred to a veterinary pathologist for further processing and evaluation. Pathologists will trim fixed tissue into pieces suitable for histologic sectioning and examination and have access to specialized tissue processing equipment needed for this work. However, if the practitioner does not collect and preserve tissue, the pathologist has nothing to work with. It is important to remember that just like any other learned skill "practice makes perfect." The more postmortem exams done, the easier they become. The more postmortem exams you have done, the better the outcome in terms of tissue collection and disease diagnosis.

Concern about the rapidity of autolysis of the nervous system is often given as a reason for not doing a neurologic postmortem. The assumption being that autolysis will preclude the collection of useful information. Of course, it is always better to collect and preserve fresh tissue, but autolysis begins at the moment of death in all tissues, not just those of the nervous system. It is possible to make meaningful gross and microscopic observations, even in tissues observed and collected 12–36 h after the death of a horse. Cooling carcasses immediately after death (below 45°F, but above 32°F, if possible) slows the process of autolysis and helps preserve tissue morphology. Horses that are febrile when they die, or carcasses kept at temperatures above 70°F, will inevitably show more signs of autolysis the longer they remain warm.

For most diagnostic purposes, specialized fixatives are not necessary. Tissues immersed in 10% neutral buffered formalin solution are adequately preserved for most histologic evaluations. The most important thing for the practitioner to remember when collecting and preserving tissue is that adequate amounts of formalin fixative have to be used or tissue will not fix properly. The usual guideline followed is to use 10 volumes of formalin fixative to one volume of tissue. Practically, this means a horse brain needs to be completely immersed in a large plastic pail of buffered formalin solution and then the pail covered or sealed (to prevent leakage and vaporization of fixative). The spinal cord should go in a separate pail filled with formalin. There is a strong temptation to attempt fixation of an entire equine brain in one to two quart containers. This is pointless and tissue will not fix properly—precluding accurate evaluation later. Small pieces of tissue (roughly the size of a 25-cent piece) must be fixed at least 24 h before they can be processed. Larger pieces, like whole brains, are generally fixed intact for at least 48 h and then trimmed carefully to allow further penetration of fixative, before final trimming and processing.

At times, it may be important to collect and freeze portions of the brain. This may be done when viral disease is suspected and when fluorescent antibody stains will be used on frozen tissue. In many state diagnostic laboratories, this is the method commonly used for rapid determination of rabies virus infection. When nervous tissue is collected for these evaluations, the practitioner should cut the brain into half, double bag in a properly labeled plastic freezer bag (which is then placed in a second labeled freezer bag), and place in a freezer. The nonfrozen portion of the brain should be immediately placed, as above, in 10% neutral buffered formalin solution. Arrangements should be made to ship this material to a diagnostic laboratory as soon as possible. At times, diagnostic laboratories may prefer to work with cold (nonfrozen) tissue, and the practitioner should be aware of tissue preferences of their local diagnostic laboratories.

Special fixatives, such as Bouin's solution, are sometimes used by veterinary pathologists to fix nervous system tissues. Bouin's solution penetrates and fixes tissue more quickly than 10% neutral buffered formalin (which penetrates roughly 1–2 mm of tissue per hour at 70°F). However,

special fixatives are not readily available to practitioners or needed for most pathologic studies. For some research studies, mixtures containing buffered glutaraldehyde are perfused into nervous system tissues in order to preserve them for electron microscopy. Again, this is for special work, not routine diagnostics.

A concern about the possibility of infectious or zoonotic disease of the nervous system can be given as a reason not to perform a postmortem examination of the nervous system. A number of simple steps should always be taken if rabies or other potentially zoonotic diseases are suspected.

First, it is absolutely mandatory to know what to do, how to do it, and who to call if rabies/zoonotic disease is suspected. Veterinarians should know what zoonotic diseases are present in their practice area and should know who to contact if exposure is suspected. This will very likely be a state veterinarian, state diagnostic laboratory, and the local department of public (human) health. It is highly advisable to know requirements for tissue submission (fresh tissue, refrigerated tissue, multiple serum samples, frozen tissue, and formalin-fixed tissue) to diagnostic laboratories—well before there is a potential exposure or illness that is creating a public health crisis.

Second, it is absolutely mandatory to keep a careful track of the names of all people potentially exposed to a suspect animal, including owners, family, farm personnel, veterinarians, veterinary technicians, laboratory personnel who handle fresh tissue/blood samples, or casual contacts. Collecting addresses and telephone numbers of these people will be important if the presence of a significant disease, such as rabies, is confirmed in a horse displaying neurologic signs.

Third, it is absolutely mandatory to collect tissues and submit them for diagnostic evaluation. Some precautions are necessary to do this safely, however.

It is important to limit the exposure of all personnel to a potentially infectious animal. The animal should be segregated from other animals and from people. As soon as is practical, if the animal is not already dead, it should be humanely destroyed and moved to an area where an adequate postmortem evaluation can take place. In many cases, this will occur on the farm and will be done by a veterinary practitioner.

Arrangements should be made, in advance, for carcass disposal, preferably by burying deeply after postmortem evaluation. Carcasses should not be transported for rendering, as this increases the risk of inadvertent exposure for anyone handling the carcass. Carcasses may be transported for incineration, but only by qualified personnel, and with explicit warnings regarding potential exposure to infectious agents.

The veterinarian and personnel who will assist the veterinarian in performing the postmortem examination always must minimize their potential for exposure to infectious agents. While it is relatively common for both horses and veterinarians to be vaccinated against rabies, at least in the United States, one should never presume that either the horse or veterinarian is immune. There are significant individual variations in the length of immunity following vaccination and in the actual antibody titer for each individual. Veterinarians who were routinely vaccinated and titered while in veterinary school may allow years to elapse before having their titer checked or being re-vaccinated. Some veterinarians will not keep their personal rabies vaccinations up to date and will be susceptible to disease if exposed.

Some veterinarians wrongly presume that horse owners are diligent in maintaining vaccinations of their horses against common, and potentially zoonotic, infectious agents. Some horse owners do not believe in or understand the necessity of regular vaccination against infectious diseases. Given the surge in popularity of herbal and holistic medical approaches, and some lay literature regarding potential "harm" of vaccinations in people and animals, some owners may not vaccinate for any disease. This has resulted in the death of horses due to preventable diseases. Other owners will attempt to save costs on husbandry and veterinary care by vaccinating their own animals. This is unfortunately an all too common practice. The quality of some vaccines from nonpractitioner sources can be quite variable, due to conditions of storage, length of storage, lot-to-lot variation, and manufacturer. Owners performing their own vaccination procedures may not administer vaccines correctly (giving a vaccination in the subcutis, for example, when intramuscular administration is required). Rabies vaccinations, and records of these vaccinations, may not be up to date, and these animals will be susceptible to disease if exposed. Without records of adequate vaccination against rabies, most public health officials

will require vaccination of exposed humans. This is costly, can be medically complicated (in the event of vaccine reactions), and can be modestly painful, especially for small children.

As a rule, when encountering an animal with a history of neurologic signs that may have an infectious (and potentially zoonotic) origin, it is best to assume there is a risk of exposure and to use personal protections. It is mandatory to completely prepare all tools and solutions before beginning the postmortem examination. Labeled containers with fixative, and bags for specimens, should be prepared ahead of time. This saves time, ensures proper labeling, and minimizes contamination of the containers. If at all possible, the carcass should be placed either on a surface that can be sanitized or a disposable tarpaulin (to contain fluids and tissues). The veterinarian should:

- Be wearing rubber gloves without holes (double glove with standard latex examination gloves or use examination gloves and standard kitchen gloves)
- Be wearing face protection to prevent exposure of mucous membranes to spattering fluids and bone chips (this absolutely will happen!). This will include wrap-around eye shield, disposable mask covering both nose and mouth, or full face shield.
- Be wearing coveralls or scrub clothes that can be removed at the end of the dissection, bagged, and then properly sanitized or incinerated (Tyvek disposable coveralls are relatively inexpensive, relatively fluid resistant, and work very well for this; they can be found in many larger hardware stores)
- Be wearing rubber boots that can be sanitized at the end of the postmortem
- Have detergent and disinfectants available to clean all surfaces, equipment, and themselves. Disinfectants must be effective against viruses, bacteria, fungi, and protozoans. An excellent guide on disinfectants is found in the *Merck Veterinary Manual*.[3] A further discussion of disinfection procedures is found below
- Have tools, pails, and brushes available for cleanup and to hold solutions. A supply of plastic bags to hold contaminated clothing such as coveralls and masks should be available. Very tough biohazard bags are available from most veterinary supply houses and are ideal for holding contaminated items. These bags are puncture resistant, leak resistant, are highly visible (red or orange are common and bear the label "biohazard"), and much more durable than standard trash bags.

METHODS FOR POSTMORTEM EXAMINATION: A PRACTICAL APPROACH

There are three common elements in all good postmortem examinations. These are preparation, developing and following a system for examination, and finalizing the case (gross and microscopic pathology reports and communication with clients and colleagues).

First, and as noted above, is preparation. The veterinarian should have:

- Taken a good medical history of the animal to be dissected, be aware of the clinical presentation and previous medical/surgical therapy, and have formulated a list of potential problems and differential diagnoses,
- Collected any ante mortem clinical pathology samples needed to help make the diagnosis,
- If possible, taken diagnostic radiographs of head, neck, and limbs to aid with case analysis and arriving at a meaningful final diagnoses,
- Be ready to document any abnormalities, both in writing and with photographs,
- Prepared the environment for the postmortem examination (see above),
- Secured any help needed for dealing with a large animal carcass and pieces of this animal,
- Have the equipment, clothing, and solutions needed (see above),
- Secured adequate lighting to work safely, to be able to see abnormalities, and for photographic documentation,
- Be prepared to disinfect the premises at the end of the examination and to properly dispose of the remains.

Second, develop and follow a system. Do every postmortem the same way, using your system. There are two possible systems. A practical procedure for field necropsy is presented here, and another method preferred by Dr Rooney and myself is detailed in our text.[4]

Most veterinarians who conduct a postmortem examination on a horse will do so "in the field." In many cases, this may literally be at a farm or boarding

facility where the horse has died unexpectedly or has been humanely destroyed. Some veterinarians may be conducting the postmortem at their practice.

When doing a "field necropsy," most veterinarians will be working with a horse lying on its side. Personal preference by the veterinarian usually dictates what side is up and which side is down. Because I am right-handed, I prefer to work with the left side of the horse on the ground. A very brief description is given below of the major elements of the necropsy before the neurologic examination, and this is followed by a more detailed description of the neurologic portion of the necropsy.

Here are some simple steps to follow.

1. Perform a thorough external examination, noting any gross abnormalities, including discharges from nose, mouth, eyes, anus, and urethra. Note the condition of the coat and any lacerations, bruises, areas of alopecia, and gross abnormalities of trunk and limbs. Examine the feet for wear and symmetry, noting whether the animal has been shod or not. Record coat color, markings, any tattoos or identification, and gender or neutering.
2. Skin the carcass, carefully, from the tip of the chin, to the anus and coronary bands. Yes, this seems like a lot of tedious work and in fact, it is. However, many lesions not easily seen from the haired side of the skin are easily visualized from the subcutis. Penetrating, but nonbleeding puncture wounds (such as bullet holes), are a good example of lesions visualized more easily from the subcuticular side of the skin. Evaluation of the skin from the subcutis also will provide information on position (postmortem hypostatic congestion is more prominent on the "down" side), duration of recumbency (areas of bruising and pressure sores), peripheral vascular congestion (sometimes seen with heat exhaustion and shock), and occasionally be useful in finding "burn tracks" associated with lightning strikes. In horses that are insured or which die unexpectedly, it is important to meticulously examine the subcutis for puncture wounds and bruising that may indicate injection sites.
3. After examining the external musculature and body walls, dissect around and remove the front and hind limbs on the "up" side. When the limbs are reflected and removed, note the condition of the brachial plexus under the front leg and collect samples of nerve. Place this in a labeled container with fixative. Note the condition of the hip joint and sciatic nerve when removing the hind leg and collect a small (2 cm) section of the sciatic nerve. Place this in a labeled container with fixative. Then, beginning at the juncture of the last rib and the backbone, dissect carefully down the wall of the abdominal cavity, following the curve of the last rib. I find that holding the knife by the handle, placing my hand and handle in the abdominal cavity, with the blade up (like a shark cutting the surface of the ocean!) and gently pushing the knife forward, usually will prevent accidentally cutting abdominal viscera. Put the limbs aside for later evaluation.
4. Allow the abdominal organs to push out of the opening. Collect any fluid samples, such as bacterial cultures, from inside the cavity, in areas not contaminated by the knife or hands. Note any fluid present (type, amount, position, consistency, and color). At this point, note the condition of the diaphragm. Unless inadvertently punctured during dissection or injured before death, this should be concave in respect to the thoracic cavity.
5. Examine the abdominal organs and note/photograph any abnormalities. I believe it is important to open the entire gastrointestinal tract on every horse, to evaluate contents, look for lesions, and, like the skin/subcutis, to get the view "from the inside."
6. Incise the top portion of the diaphragm, adjacent to the top of the last rib. Loss of negative intrathoracic pressure will allow air to enter. Look inside the thoracic cavity for any gross abnormalities and collect samples needed for later evaluation, including samples for bacterial culture. Note any fluid present (type, amount, position, consistency, and color).
7. Incise the base of the tongue at the mandible, penetrating into the oral cavity, and then strip back, using sharp and blunt dissection, the tongue, trachea, esophagus, thyroids (collect these and place immediately in fixative—they tend to get lost easily), to the thoracic inlet. Using rib cutters (heavy-duty pruning shears), cut the ribs in two places—at the junction with the spine and at the junction with the sternum. Remove this side of the rib cage; examine it and the viscera in the thoracic cavity. Remove these tissues ("the

pluck") that includes the tongue, upper airway and esophagus, lungs, heart, thymus, and mediastinum. Note and photograph gross lesions. Continue dissection of heart and lungs.

8. This is a good point to stop and take a break to reflect on whether the lesions seen to this point help explain the clinical signs noted in this horse prior to death. Make notes, take additional photographs for documentation (include labels of time, date, and animal identification), collect tissue samples, and place them in fixative (see above). As a rule, it is always a reasonable idea to collect small samples of major organs, even if there are no visible lesions, for later diagnostics. These will include liver, kidney, spleen, adrenals, lung, heart, skeletal muscle, tongue, representative sections of the gastrointestinal tract, and pancreas. Dispose of tissue safely before proceeding.
9. Turn the carcass over and finish skinning and evaluation of skin, subcutis and body wall, remove legs (set aside), and rib cage.
10. At this point, specific attention is directed to dissection of the central nervous system. Trim muscle and connective tissue from the spinal column, from the base of the neck to the cauda equina. Carefully dissect around the cauda equina at the base of the spinal column.
11. Disarticulate the head from the spinal column at the atlanto-occipital junction.
12. Skin the head, note any gross abnormalities, and carefully remove the eyes; place these in fixative.
13. With a saw, cut the skull around the brain.
14. With hatchet/axe and hammer, crack skull and peel back, revealing the brain. Note, record, or photograph any abnormalities of the meninges and collect fluid samples for bacterial culture, if indicated.
15. Tip the head nose up, allowing the brain to pull backward and down under its own weight, and then tease/cut the brain out, severing the cranial nerves. It is likely the pituitary will remain lodged in the sella turcica, having pulled loose from the stalk of the pituitary. Gently dissect around the pituitary, remove it intact, examine it, and place it in a labeled container with fixative. Place the appropriate portion(s) of the brain in fixative (see above). If fresh or frozen tissue is to be submitted for diagnostic evaluation, collect these samples prior to immersion in fixative. Put them in labeled, sealed double plastic bags, with identification of horse, time, and date noted.
16. Examine the oral cavity, guttural pouches, and other portions of the skull for lesions. Note and record or photograph these.
17. There are three common approaches for examining the spinal cord. Each has merits and shortcomings, but all are better than not examining the spinal cord. Any of the following methods are made more easy by suspending the carcass, such as from a tree, overhead beam, or front-end loader.

    Strategy 1: The spinal column is sawed in cross-section at several locations. This sawing will cut the spinal cord. Typical points of sawing are between C2 and C3, T1 and T2, T4 and T5, T10 and T11, L1 and L2, L4 and L5, and at the L–S junction. The cut ends of the cord are examined and any abnormalities noted. At the points of sawing, the cord is gently pulled by the meninges and cut with scalpel approximately 1–2 cm in back of the sawed edge (the morphology of which is damaged by sawing). These sections are placed in separately labeled containers, by anatomic site, with fixative. This is the most common, and acceptable, method used by practitioners during field necropsies. This method is very useful for tissue collection, but does not sample the entire cord, allow for focal lesions to be detected and sampled, and may damage tissue for morphologic evaluation.

    Strategy 2: The spinal column can be sawed into pieces, as above, these pieces can be cooled (just above freezing) and packed in a cooler, and transported immediately to a diagnostic facility with a band saw, where the spinal column sections can be longitudinally sawed, the cord collected intact, and after examination can be placed in fixative prior to further trimming. This strategy requires communication with the laboratory and arrival of specimens within 6 h of postmortem for best results.

    This method is used by diagnostic pathologists in many laboratories. It requires special equipment and skill. It allows anatomic orientation of the cord to be preserved, facilitates detection of abnormalities, and allows exhaustive trimming and sectioning when looking for lesions. The author has used this method and has at times prepared and examined over 100 cross-sections of spinal cord looking for minute lesions associated with equine protozoal myelitis (EPM).

Strategy 3: This is a variant of Strategy 2 and is rarely used. It requires a lot of skill and is dangerous for most people since it involves the use of a chain saw. In this method, the cord is collected after all soft tissues have been dissected of the dorsal part of the cord, and then by essentially performing a dorsal laminectomy along the entire length of the spinal column with the chain saw. Needless to say, it is very easy to cut into and damage the cord with the chain saw if one is not careful. Personal injury is also a possibility as this is not the intended use of the chain saw; it is best to stick with Strategy 1 and Strategy 2!

18. Examination of peripheral nerves requires careful dissection along the length of the nerve. These nerves frequently run through muscle and fascia and it may be time-consuming (but rewarding) to follow them from a point of origin near the trunk of the body to the nerve endings at the distal limb and tip of the tail. Prior to dissection, it is important to consider if there are any injuries or musculoskeletal lesions surrounding the peripheral nerves that need to be examined during the course of dissection. Nerve dissection requires a gentle touch, handling of the connective tissue around nerves (not the nerve itself), and attention to obvious abnormalities. Photographs documenting suspected areas of injury are immensely helpful in later discussions with pathologists, with horse owners, and with insurance agents.

    Finally, dissect and examine the limbs, including opening the joints. In some cases, this is simple, requiring splitting of the joint capsule and major ligaments. In other joints, like the tarsus, this is both time-consuming and difficult, given the complex bony articulations. Again, it is important to continue to focus on determining all contributions to presumed neurologic signs, including those due to bone, tendon/ligament, and muscle injury.

19. When working with foals, several additional points should be considered in conjunction with the postmortem examination:
    - Is there a history of dystocia with the mare?
    - Is there a history or observations of dystocia with the birth of this foal?
    - Were there any exposures to vaccines, infectious agents, or toxicants, such as fungal feed contaminants or toxic pasture plants, at any time during gestation?
    - Was the foaling abnormal in any way?
    - Is the placenta available for evaluation and is it normal or abnormal?
    - If the placenta is available, portions should be saved for microbial culture and also fixed for histologic evaluation.
    - Did the mare have an uneventful pregnancy?
    - Have any foals born to the mare or stallion previously had birth defects, including neonatal maladaptation?
    - Did the foal suckle normally or was there evidence of failure of passive transfer of colostral antibodies?
    - If there is gross evidence of one type of birth defects (such as limb or facial deformities), it is very worthwhile to search for others during the postmortem examination.
    - Microscopic lesions associated with neonatal hypoxia may be difficult to find histologically,
    - Evaluation of joints and umbilicus for the presence of sepsis are a mandatory part of the postmortem examination.

Many of these additional points are addressed by questioning of the owner before the dissection. Answers to these questions help the practitioner and pathologist when interpreting lesions and preparing reports. Postmortem examinations on foals are done in the same manner as adult horses.

The third element of the postmortem examination is as important as the first two. You must document gross lesions. Gross lesions of the nervous system can be simply and adequately described by noting (in writing—on the medical record) size (in comparison with normal), shape, color, gross consistency (soft, firm, gelatinous, crumbly, and clot-like), and anatomic position (spinal cord segment, etc.). Nothing fancy is needed, and this is the basis for all gross pathologic description. Noting the extent of a lesion in terms such as focal (single, small), multifocal (lesions scattered about in tissue), or diffuse (affecting the entire tissue).

GROSS ABNORMALITIES OF THE NERVOUS SYSTEM—SOME WORKING GENERALIZATIONS

It is important to know normal anatomy and morphology of tissues in the central nervous system, so that one can adequately detect and describe abnormalities. Gross abnormalities found during the postmortem examination can be very helpful in

determining causes of sickness and death in horses; the definitive diagnosis of many cases relies on both gross and microscopic evaluations, and the practitioner should never "guess" on diagnosis based only on gross appearance of lesions. A few generalizations about disease, based on gross appearance, may be useful.

Changes in color of the brain or spinal cord can indicate trauma, hemorrhage, degeneration, or inflammation. Normally, the color of fresh equine brain and spinal cord is pearly-white to tan. Brains and cords that are undergoing autolysis may become grayer with advancing time (and also become much softer as degradative enzymes break down tissue). Diffuse vascular congestion, due to hyperthermia (inflammatory disease or heat stroke), may cause the meninges of the brain and cord to be red-purple. Red or purple foci may indicate areas of vascular disruption and hemorrhage, and there are many causes of this, ranging from trauma to vascular leakage associated with coagulopathies. Foci with dark red, brown, or gray discoloration, in which there is also softening of brain or spinal cord tissue, may indicate hemorrhage, malacia, infarction, or even the presence of a neoplasm. Many diseases can be expressed by the same changes in color, and these areas sampled for further histopathologic evaluation.

Normal, fresh brain and spinal cord have a soft but spongy/rubbery consistency. The longer brains and spinal cords remain between 25 and 38°C (ambient room temperature to physiologic temperature) after death, the more they will undergo autolysis and soften. The brains of animals that have suffered from hyperthermia may be soft, to the point of liquefaction, even when collected within 1–2 h of death.

In some diseases, changes in consistency are very important clues to the final diagnosis. A classic example of this is the gelatinous liquefaction of areas of the brain in horses exposed to the toxin fumonisin (moldy corn poisoning). Foci of necrosis, which can be caused by many things (infarction, trauma, and infections for example), are soft and discolored due to the release of enzymes from brain and cord tissue and infiltrating inflammatory cells, if present.

Notable changes in symmetry and position also can be useful in finding lesions. Both the brain and spinal cord display a high degree of bilateral symmetry. This also applies to the morphology of the ventricular system that circulates fluid in the brain, and to the vertebral bodies surrounding the spinal cord. Deviations from symmetry, or malpositioning [as might be seen with atlanto-occipital malformations in Arabian horses or cervical vertebral instability (equine Wobbler syndrome)], are good indicators of lesions/disease at those sites.

Changes in normal size are important. Dilation of the ventricles of the brain may be indicators of some lesion or disease process that has interfered with fluid production and flow. Many veterinarians understand that dilated ventricles (hydrocephalus) compress surrounding brain tissue into the noncompressible bones of the skull and spinal cord, leading to atrophy and degeneration of brain tissue. It is not uncommon to see subtle-to-very remarkable enlargements of the pituitary gland in horses with equine Cushing's disease.

Another generalization about size and position is important to consider. In general, the larger the lesion, the more significant and serious the disease and clinical signs are. Minor cases of hydrocephalus or small meningeal cysts may be incidental findings in horses without overt signs of nervous system disease. Diffuse inflammation and hyperthermia associated with infection by encephalitic viruses (herpesvirus, equine encephalitis viruses, and rabies) produce profound signs and lesions. Of course, the position of lesions may dictate clinical signs (blindness due to pressure on the optic chiasm from the growth of a large pituitary adenoma is an example). Localizing lesions, based on ante mortem clinical signs, is an important part of analyzing cases and performing diagnostic postmortem exams.

A final generalization is one we are all familiar with. The brain and spinal cord are encased in protective bone. Space occupying lesions (such as abscesses and neoplasms) and processes that result in brain/cord swelling (edema, inflammation, and neoplastic disease) readily produce neurologic signs and tissue damage.

WORKING WITH THE NEUROPATHOLOGIST

Most practitioners are going to rely on the services of a pathologist in helping to sort out lesions seen in horses with neurologic disease and in helping to finalize cases. The practitioner and pathologist form an important team in diagnosing, treating, and in some cases, preventing disease. Both parties

need to cultivate this relationship and foster good communication.

Once pathologists receive tissues and observations from practitioners, it is common for them to call to discuss the results of the gross postmortem examination with the practitioner and to review points raised in the history and ante mortem examination.

Well-fixed tissue specimens are carefully trimmed by pathologists and then prepared for histologic evaluation. This trimming and preparation may take several days after tissue is received. If fresh or frozen tissue is submitted, especially for priority evaluation of rabies or other agents, fluorescent antibody testing on frozen sections is generally completed with 24–48 h.

Most routine sections are stained with hematoxylin–eosin, a general purpose set of stains that will stain nuclei purple/blue and proteins (cytoplasm) pink/orange. This stain is usually adequate for diagnostic evaluation of most cases.

Several types of special stains are used in neuropathology. Stains containing silver and gold have an affinity for nerve tissue and can be used for contrasting neurons and axons from surrounding connective tissues. A host of antibody-based stains (fluorescent antibody and immunohistochemical stains) are used to show localization of proteins or infectious agents in brain and spinal cord. These stains typically contain an antibody directed against some organism or cell component (such as epidermal growth factor receptor [EGFr] or glial fibrillar acidic protein [GFAP]) and a chromogen that either fluoresces or develops a pigment that can be viewed microscopically. These stains are extremely helpful in definitive diagnosis of infectious diseases of the nervous system (like rabies) or to differentiate specific types of tumors.

Interpreting the Pathologist's Report

Pathologists typically report findings as a series of morphologic diagnoses and final summary statements which relate the diagnoses with clinical signs, history, and gross lesions. There is a rather consistent "language" and sentence structure of most pathology reports, since many veterinary pathologists are trained in diagnostic terminology originally developed through the Armed Forces Institute of Pathology and adopted both by veterinary pathology training programs and by the American College of Veterinary Pathologists. At times, pathology reports may be difficult to "decode," and it is wise to ask for a more descriptive summary that contains less overt "pathologese."

Some terms used by pathologists are common. "Malacia" typically refers to necrosis and degeneration of brain tissue and morphology. Terms containing the suffix "itis" indicate inflammation. "Encephalo-" refers to brain and "Myelo-" to spinal cord. The terms "leuko-" refers to the white matter (myelin-containing portions of the nervous system) and "polio" to gray matter (neurons and neuropil).

It is beyond the scope and purpose of this chapter to include descriptions of the many primary and secondary diseases of the nervous system of horses. There are many excellent reference texts with this information. The equine practitioner may want to consider purchase of any of the several new veterinary pathology textbooks on the market or specialty texts devoted entirely to the subject of equine pathology.

Most neuropathologists will send a report to the referring veterinarian that gives a brief review of the clinical and gross pathology findings, as well as a more extensive description of microscopic lesions. Pathologists vary widely in the style and content of these reports. Some may prefer to simply list the tissues and enter short morphologic diagnosis, containing the elements of lesion type, severity, distribution, and an indication of chronicity. An example of this type of reporting might be:

"Spinal cord: Acute, severe, diffuse suppurative meningitis." One translation of this into more common terminology is "there is severe, diffuse acute inflammation of the meninges and this is manifested by the presence of neutrophils, perhaps other inflammatory cells, and necrotic cell debris (things that make "purulent" material, i.e., "pus").

Other pathologists may prefer to write reports as a narrative, using more common language (the translation above is an example of this style).

A number of terms are commonly used by all pathologists, especially when describing changes in the morphology of nerve cells. It may be necessary to review the basic organization of the nervous system in order to understand common pathology terms indicating the presence of disease. A few of the common pathology terms used frequently by pathologists are included below. A few simple working definitions and an indication of significance of the terms lesions are included.

"Neuropathy"—this can refer to the gross and histologic changes seen in nerve tissue, or more specifically may indicate lesions in nerve cells. The term neuropathy says something is wrong, but lacks precision in indicating what and where the problem is.

"Axonopathy"—here there are morphologic changes in the shapes of axons. Two very typical axonopathies are seen in horses. In one, there is shrinkage of the axon within the axon sheath. This may be indicative of damage to nerve cell bodies upstream or overall nutrient availability for nerve cells and axons. Another common axonopathy is swelling of the axon within the sheath. This gives the appearance of enlarged axon spaces. In reality, this swelling may be the result of fluid accumulation within and around axons, but the fluid is not easily visualized (low protein content) or is leached during histologic processing.

"Myelinopathy"—loss of integrity of the myelin sheath surrounding axons. This can be the result of nerve cell body and axon damage, or may be a primary lesion specific to a disease. In dogs, for example, canine distemper virus produces a myelinopathy resulting in dissolution of myelin. Similarly, multiple sclerosis in people has a myelinopathy as one important disease component. Since myelin protects axons and regulates nerve impulse conduction integrity, a loss of myelin has significant consequences for affected cells.

"Wallerian degeneration"—this term refers to degeneration of axons and myelin distal to an injury.

"Perivascular cuffing"—this indicates the presence, usually of inflammatory cells, around blood vessels in the brain and spinal cord substance. Many pathologists believe this lesion probably represents a loss of integrity of the blood–brain barrier at these sites. A number of viral and bacterial infections of the central nervous system have foci of perivascular cuffing as primary lesions.

"Perivascular edema"—this is seen fairly commonly, both as an indicator of the presence of disease and also as an artifact of fixation. One must interpret this with caution. The lesion described usually refers to clear spaces surrounding blood vessels and nerves.

In this age of intensive electronic communication, there is no reason that anyone receiving a pathology report should hesitate, even for an instant, to call the pathologist who wrote it to get a better understanding of the contents of the report. Translation: you need to pick up the phone!

SUMMARY AND FINAL THOUGHTS

Primary and secondary diseases affecting the nervous system of horses are common causes of morbidity and mortality. Every practitioner can become competent in diagnosing these diseases with clinical and pathologic evaluations. However, if one does not look, one does not find. Practitioners are strongly encouraged to hone skills for examining the tissues making up the nervous system and for developing good working relationships with pathologists and diagnostic laboratories. Together, this team will find the answers to many problems and help many horses and their owners.

REFERENCES

1. Robertson JL. 1996. Nervous system. In *Equine Pathology*, edited by Rooney JR, Robertson JL. Ames: Iowa State University Press.
2. Rooney JR. 1998. *The Lame Horse*, Neenah: Russell Meerdink Co Ltd.
3. *Merck Veterinary Manual*, edited by Kahn CM, 2153–8. Philadelphia: National Publishing, Inc.
4. Rooney JR. 1996. Autopsy method. In *Equine Pathology*, edited by Rooney JR, Robertson JL. Ames: Iowa State University Press.

Section III:
Specific Disease Syndromes

13
Viral Diseases of the Nervous System

Lutz Goehring

There are few known viral causes for central nervous system (CNS) infection in horses. Only two viruses have been implicated as causing equine neuropathy without initially affecting other organ systems: rabies virus and Borna virus. These two viruses have developed a distinctive tropism or predilection for the CNS. All other known viruses begin with a generalized infection, which may only involve the CNS in some exposed horses. Depending upon exposure and immune status of the individual horse, the disease that follows a viral infection may be subclinical, it may be limited to body systems excluding the CNS, or it may include the CNS. When confronted with a horse that exhibits clinical signs of a viral encephalitis, it is extremely important to evaluate the entire group of horses which are in close contact with the affected horse. Those findings will help form a conclusion as to the etiology of the CNS disease.

Several anatomical and functional structures of the CNS may be involved: the brain, spinal cord, meninges, gray matter, white matter, and vascular and/or support structures such as endothelium and glial cells. Which structures will be infected first depend on the route taken by the virus to enter the CNS, or the location at which the virus breaches the blood–brain barrier (BBB). Some viruses exclusively cause damage to the support structures of the CNS. Equine herpesvirus (EHV), for example, causes endothelial cell pathology at the BBB first, resulting in subsequent damage to the adjacent CNS due to hypoxia and ischemia.[1,2]

An encephalitis (brain) or myelitis (spinal cord) is defined as a disruption of central nervous function due to a direct structural or inflammatory process within the nervous tissue parenchyma. An encephalopathy or myelopathy is the result of damage to non-nervous structures in the vicinity of nervous parenchyma.[3] In general, viral encephalitis is an emergency situation. The affected horse may be dangerous to handle, and there is potential risk for spread of disease to healthy horses, other animals, and in some cases to people. Horses with a fever and clinical signs of neurological disease should be considered contagious until proven otherwise. These horses should only be managed under a structured biosecurity protocol.

DIAGNOSIS

Diagnosis of viral encephalitis or myelitis is based on:

- History (including regional disease occurrence)
- Clinical examination
- Cerebrospinal fluid (CSF) analysis and serology
- Medical imaging and functional testing
- Postmortem examination

Peracute deaths or horses that died during an outbreak of unknown disease may be diagnosed by postmortem examination and are extremely valuable in supporting or consolidating a tentative diagnosis. A current and comprehensive list of recommended laboratory diagnostic tests for most of the equine viral infections, their validation, reference laboratories, and standard operating procedures can be found on the website of the Office International des Epizooties (http://www.oie.int). These recommended diagnostic tests are incorporated into the following sections where the individual viruses and their pathogenesis are discussed.

Medical History

Medical history should include information about the geographical location of the horse and its recent travel history, and whether the affected horse is new to a specific area. This is important information because regional pathogens, or pathogens a horse may have encountered during traveling, should rank higher on a list of differential diagnoses. It is important to determine the onset and progression of clinical signs in the affected horse and whether a similar presentation was observed previously on the same premise and under similar seasonal conditions. A good medical history also includes information on health status of other horses in the vicinity of the affected animal. Several horses may show (or have a history of) similar clinical signs or a fever. Medical history provides a vaccination history and may reveal risk factors associated with a specific infectious agent or disease.

General and Neurological Examinations

Infection with a virus usually causes a fever. Careful questioning will determine whether there is currently more than one horse with a fever, or if there is a recent history of febrile horses on the premise. Fever coincides with replication of the virus at the entry site, specific organ infection, or viremia. During viremia, virus can be found either free in the plasma fraction of blood, or in one of the leukocyte cell fractions. The latter event is referred to as a cell-associated viremia. Some viral diseases such as rabies and equine infectious anemia virus (EIAV) have a long incubation period in horses and a subtle onset. An initial febrile period may have been missed, and only a single horse is typically affected.

Viruses that affect the nervous system generally differ in their predilection for specific parts of the CNS. However, there can be significant overlap between clinical signs. Routinely, viruses tend to cause rather symmetrical, multifocal, or diffuse lesions—an observation which helps to differentiate viral illness from those caused by protozoans, bacteria, or nematodes.

CSF Analysis

CSF analysis is the key to further diagnostics in most viral encephalitis cases. CSF analysis is the clinical test closest to a histological examination of central nervous tissue. However, production of CSF is continuous, which may dilute antigen or antibody concentrations, and therefore limits its diagnostic properties. CSF collection has two purposes: to identify antigen or specific antibody by means of culture, polymerase chain reaction (PCR), and appropriate antibody detection test [enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody test (IFAT)], and secondarily to look for changes in protein concentration, cellular composition, extent of damage to the BBB, enzyme activity [creatine kinase (CK) and lactate dehydrogenase (LDH)],[4,5] and inflammatory mediator profiles by means of mRNA PCR amplifications.[6] The most frequently observed changes of CSF due to a viral encephalitis/encephalomyelitis are a mononuclear pleocytosis and an increased protein concentration.[5]

Although all virus infections influence the peripheral blood cell count, it is not diagnostic for viral disease in general nor for a specific viral disease. Leukocyte dynamics will vary based on the time course of the infection, the infectious dose, and the responsiveness of the host's immune system. In general, it may be best described by a lymphopenia/neutropenia followed by a tendency to overcompensate, resulting in a mild lymphocytosis with or without neutrophilia.

Antibody detection tests focus on IgM or IgG detection using ELISA or immunofluorescent antibody-staining techniques. IgM detection is preferred in current tests because this antibody class is produced early during the course of disease. In addition, due to its larger size when compared to the IgG molecule, it is less likely to diffuse across the BBB and it will not be present in CSF in the vaccinated, uninfected horse.[7] Certain viruses affect the integrity of the BBB. The albumin quotient (AQ) can be calculated based on albumin concentrations in serum and CSF. The AQ can help to increase specificity, in other words, to reduce the number of false-positive specific test results. An IgG index is a calculation based on the amount of serum versus CSF total IgG concentration, which helps to distinguish between intrathecal antibody production and antibody leaking into the CSF compartment due to a disrupted or inflamed BBB. These tests are discussed in greater detail in Section 1, Chapter 2.

Medical Imaging and Functional Testing of the Brain

Medical imaging [(computerized tomography (CT) and magnetic resonance imaging (MRI)] and

functional testing (electroencephalogram, EEG) may serve as additional diagnostic procedures. These techniques may help to distinguish between a localized, multifocal, or a diffuse intracranial disease process.[3,8] CT and MRI have been advocated as important diagnostic tools in cases of human viral encephalitis. However, the use of CT/MRI for the equine neurological patient is still very limited to a few well-equipped referral hospitals. Because the gantry of CT/MRI usually does not allow evaluation caudal to the mid-cervical region of an adult horse, these diagnostic procedures are limited to those patients with clinical signs of intracranial disease. Viral encephalitic lesions may be too small to be detected, or they may appear only as nonspecific intracranial edema. The few reports that utilized CT/MRI evaluation of horses presenting with intracranial disease[9–12] describe bacterial abscesses in the cerebrum, brainstem, or pituitary gland; temporomandibular osteoarthropathy with subsequent fracture of the temporal bone; nigropallidal encephalomalacia, and congenital hydrocephalus.

Postmortem Examination

If a horse is rapidly deteriorating due to viral CNS infection, such that recumbency or automutilation becomes a problem, or if several horses are affected in an outbreak situation and an initial work-up has not produced a definitive finding, then (histo)pathological evaluation of the CNS may provide a diagnosis. With viral encephalitis, a macroscopic evaluation may not answer urgent questions. Usually immunohistochemistry,[13] hybridization probes (*in situ* hybridization),[14] and PCR amplification will help with further diagnostics. Immunohistochemistry uses labeled antigen-specific antibodies that bind to surface proteins of infected cells or directly to antigen. Hybridization probes are labeled with congruent DNA or RNA sequences that attach to antigen-specific nucleic acid sequences on tissue sections, which can then be evaluated under the microscope for fluorescence. For PCR amplification, DNA or RNA has to be extracted from tissue which then can be amplified using antigen-specific primer sets. All of these techniques require at least a suspicion of the causative agent, a group antigen, or group-specific probe to confirm infection. Suspected but unknown causes of viral encephalitis/myelitis should be investigated by tissue culture on appropriate equine cell lines.

GENERAL RECOMMENDATIONS FOR TREATMENT

The stall should be separated/isolated and quiet, with deep bedding and padded walls. A central hoist, properly supported in the ceiling, is beneficial if slinging becomes necessary. Bright sunlight should be avoided. The horse's ability to eat and drink should be evaluated repeatedly. Brainstem involvement can influence mastication and swallowing. Horses with a head tilt may experience difficulties with eating from the ground, or from a position where they have to turn their head against the direction of the tilted position. Adjustments to feeding and watering routines should be made for such animals.

Horses which are recumbent have to be turned at least every 4–6 h, and they should be placed on soft bedding to avoid decubital ulcers. With horses that are struggling while recumbent, the first objective should be to determine why they are so restless and corrections made to facilitate comfort if possible. The horse may attempt to stand, which may be aided for short periods by using a sling. Slings should be used carefully, however, and not all horses will tolerate them. The sling must be well-fitted, and not compromise respiration. Ideally, the sling will simply provide the opportunity for the horse to rest intermittently and aid its balance. Horses that cannot support large portions of their weight are best not put into a sling. Horses with a head tilt are usually very uncomfortable when they are forced to lie on the body side which is contralateral to the affected side. Increased intracranial pressure may cause involuntary, compulsive movements and seizure activity, which demand sedative drugs and efforts to decrease intracranial pressure.

There has been a great deal of discussion about the intravenous use of osmotic agents such as mannitol and dimethyl sulfoxide (DMSO) under circumstances of viral intracranial disease. A generalized recommendation cannot be made, because these decisions strongly depend on the clinical presentation and the course of the disease in the particular case. Systemic nonsteroidal antiinflammatory drugs should always be given in suspect viral encephalitis/myelitis cases to curtail the inflammatory cascade. The use of corticosteroids in viral encephalitis/myelitis cases should also be determined on a case-by-case basis. Corticosteroids have an immunosuppressive effect on the patient, which

has been thought to allow a virus to continue replication and tissue propagation. While this has not been examined in the horse with viral disease, it has been documented not to occur in other species with viral encephalitis.[15,16] Corticosteroids also have a substantial effect on the inflammatory cascade and free-radical scavenging in the CNS. It is advisable to combine corticosteroid therapy with antiviral therapy, if available and if *in vitro* efficacy of the drug has been demonstrated. For some viral diseases, there is antigen-specific antibody therapy available (e.g., WNV). However, these antibodies can only be effective at an early stage when antigen is present in the vasculature or at the site where virus penetrated the body. Once antigen has translocated into the CNS, or is transported intracellularly, antigen-specific antibodies will not be very effective. Vitamin E as an antioxidant, as well as thiamine, plays an adjunctive role in virus encephalitis/myelitis therapy. Antiinflammatory therapy of the CNS is further discussed in Section 1, Chapter 4.

CSF phoresis is a poorly explored technique which may be beneficial in some cases of viral encephalitis/myelitis. The principle behind this technique is a gradual and continuous removal of CSF, which potentially facilitates the removal of infectious agent and inflammatory mediators, while increasing the production of CSF at the choroid plexus. There is limited experience with this technique in horses affected with Borna disease virus (BDV); however, attempts using the short-term application of a subarachnoidal catheter system inserted lumbosacrally in the horse are technically possible.[17]

GENERAL COMMENTS ON PREVENTION

Vaccination of horses and the potential virus reservoir (other livestock) in combination with minimizing exposure to vector or reservoir play a key role in preventing disease. Viruses need the machinery of viable host cells for their reproductive cycle. The group of enveloped viruses requires an intact envelope for host cell penetration. However, the envelope structure is easily destroyed by environmental factors such as desiccation, freezing, UV light, and detergents. Hence, enveloped viruses require a short transmission distance which stresses the benefits and the importance of a good biosecurity protocol with adequate barrier precautions (gloves, protective gowns, hand sanitation, and fomite transmission).

Table 13.1 lists the viruses so far known to affect the equine nervous system. Biologists and virologist are quite certain that there are more viruses with potential for CNS pathogenesis secluded in well-defined habitats. The West Nile virus (WNV) epidemic which started in 1999 in the United States has demonstrated how quickly a virus can spread from a regionally confined area when it is introduced into an immunologically naïve continent.

Viruses are discussed in the sequence listed in Table 13.1. Viruses with a primary neurotropism without the initial involvement of other body systems will be discussed first. Then, viruses with neurotropism besides other organ systems will be listed, followed by viruses with a tropism for CNS-associated tissue, where a neuropathy develops as an innocent bystander reaction. The largest group of viruses known to affect the equine CNS consists of arthropod-borne viruses (ARBO viruses), and in particular viruses of the group of Togaviridae, Flaviviridae, and Bunyaviridae.

VIRUSES WITH PRIMARY NEUROTROPISM

Rabies Virus—Rhabdoviridae

Genotype 1 (classic) and bat variants (genotypes 2, 5, 6, and 7)
Characteristics: ARBO: no, enveloped: yes
Reservoir and transmission: dogs, foxes, raccoons, skunks, and bats
Endemic to: worldwide distribution with very few exceptions

Rabies virus is still one of the most frequent causes of viral neuropathy in humans. This is due to the virus' worldwide distribution, and the usually fatal course of the disease. Rabies encephalitis is probably one of the oldest described viral diseases. Dogs in ancient Mesopotamia and Egypt were associated with transferring a disease to humans which caused change in people's behavior. Two genotypes are described: the classic genotype, which has greater pathogenicity, and the "bat variants."

Epidemiology and Risk Factors

Virus reservoirs for genotype 1 are diverse, and a regional reservoir usually predominates. Foxes,

Table 13.1. Viruses Associated with Central Nervous Disease in Horses

Clinical Classification	Virological Taxonomy	Virus Reservoir/Vector	Zoonotic potential
Primary neurotropism	Rabies virus (Lyssa virus)	Regional differences in virus reservoirs: dogs, raccoons, foxes, skunk	Yes
Primary neurotropism?	Borna disease virus (Bornaviridae)	Possibly small rodents (shrews)	Unknown
Neurotropism among others			
ARBO A (Togaviridae)	Eastern, Western, Venezuelan encephalitis virus	Birds/ mosquitoes	Yes
ARBO B (Flaviviridae)	Japanese encephalitis virus, West Nile virus, Ilheus virus	Pigs, birds/mosquitoes	Yes
ARBO C (Bunyaviridae)		Small rodents, lagomorphs, birds, others?/ mosquitoes	Yes
Tropism to CNS-associated structures	Equine herpesviruses (1 and 4) (alpha-herpesviridae)	Latent infections in equids	No
	Equine infectious anemia (Retroviridae)	Chronically infected horses/horse fly (deer fly)	No
	Hendra and Nipah (Paramyxoviridae)	Fruit bats, pigs	Yes

raccoons, skunks, dogs, and coyotes are described as natural virus reservoirs. Bats worldwide are the reservoir for genotype 2. New World bats, however, can also be reservoirs for genotype 1. The role bats play in the epidemiology of rabies has not been fully described.

Risk factors for horses to contract rabies include residence in an endemic rabies area, 24-h access to pasture, and no vaccination history against rabies virus. There is no breed or gender predilection, and young horses are more commonly affected.

Pathogenesis

Horses become infected following the bite of a rabid animal. So far, the transmission of genotype 1 from bats to horses or livestock has not been described. Classic rabies virus (genotype 1) has a sylvatic virus reservoir, which is a regional wild mammal (wild dogs, foxes, coyotes, skunks, and raccoons).

The pathogenesis of rabies is characterized by three distinct periods. Phase 1 is the ascending or centripetal phase where virus is transported toward the CNS; phase 2 is the period of multiplication of virus within the CNS; and phase 3, which is also called centrifugal phase, is that period where virus leaves the CNS and infects other organs in the body. Centripetal, or ascending transport of virus, occurs after the bite of a rabid animal, and after a short cycle of replication in muscle cells at the bite site. Then, virus enters motor and sensory neurons via their acetylcholine receptors. Paresthesia at the bite site may develop which results in rubbing, biting, or automutilation. With the neuron entry, rabies virus leaves its envelope and travels toward the CNS by axonal transportation into the cell body of the infected neuron, which has a position in the CNS. This is the mechanism of rabies virus' impressive entry into the CNS.

Phase 2 in horses is characterized by extensive replication of virus in the limbic system, adjacent parts of the brain, and spinal cord. The extensive replication in the spinal cord is different from the pathogenesis in humans. Clinical signs are associated with phase 2 of a rabies virus infection. Phase 3 or the centrifugal or descending spread of virus follows phase 2, and is again characterized by neuronal transportation of virus into highly vascularized organs. Among these are the salivary glands, which facilitate the virus' spread and excretion into the environment, or into a new host. Because phase 2 is the period with the most dramatic clinical signs, most horses will be euthanized during that time.

A time frame for the three phases in the horse is as follows: phase 1, probably several days to weeks; phase 2, actual phase where clinical signs are noticed, last on average up to 7 days; phase 3, seems to be curtailed by decisions regarding euthanasia of the horse, or sudden death.

Clinical Signs in the Horse

There is no CNS disease described where the clinical presentation can be more diverse. For an overview of clinical signs of rabies infection, see Table 13.3. Clinical signs can vary from muzzle tremors and lethargy, to severe ataxia, behavioral disorders, and seizures.[18] The most common owner's complaint is "colic," or lameness. The spinal cord is most commonly affected in horses, and perhaps reflects the most common location (limbs) for inoculation. This is different from the location of the primary infection in humans.[19] Involvement of the brainstem is seen less frequently, followed by rare cerebral infection. Most commonly encountered clinical signs are therefore (ascending) ataxia and hind limb paresis/paralysis combined with loss of tail and anal sphincter tone, loss of sensory perception of the limbs, and muscle tremors.[20] These signs may be noted in combination with a wound on the limbs. In addition, but also independently, brainstem signs are described including cranial nerve dysfunction such as blindness, abnormal vocalization, drooling, and dysphagia. The "furious" or cerebral form is rare in the horse, and clinical signs such as convulsions, aggressiveness, photophobia and hydrophobia, tenesmus, circling, and hyperesthesia are attributed to this form. Incubation period, time to onset of clinical signs, (sequence of) clinical signs, and survival time depend on the site of the bite wound, the inoculated viral dose, and the pathogenicity of the viral strain.[20] In one prospective virus challenge study which utilized intramuscular injection into the masseter muscles, the average incubation period was 12.3 days, with a morbidity duration of 5.5 days before euthanasia.[18] The incubation period is likely to be longer if the inoculation (or bite) occurred on a distal limb.

Typically, a single horse out of a group is affected. The affected horse is likely to be febrile, but may not be, and absence of fever should not eliminate rabies as a possibility.

Rabies is an invariably fatal disease. It takes usually between 5 and 10 days until death occurs or euthanasia is performed. Its clinical course may be prolonged in cases of intensive nursing, which increases the risk of transmission of virus into humans, because it becomes more likely that phase 3 will be reached. There is no remedy to date that stops viral replication in the CNS.

Diagnosis

There are no reports on ante-mortem diagnostics performed in horses or livestock. In humans skin biopsies of the bite site, hair follicles, corneal imprints, and CSF have been described as test material for rabies detection.[21] Clinical signs in the horse precede the centrifugal spread, which probably does not allow virus detection in cornea or saliva. CSF analysis of rabies-infected horses shows a mild-to-moderate lymphocytic pleocytosis in combination with a mild increase in CSF protein concentration and mild xanthochromia.[20] There are currently no diagnostic tests that are consistently accurate or fast enough to be of practical use. Reports of antigen detection in CSF by ELISA, fluorescent antibody test (FAT), or PCR have been employed, however, with false-positive and false-negative results. A neutralization test (serum and CSF) is available, however, due to the rapid course of the disease, and in light of vaccination titers it may be of little value. Clinical signs that remain stable for more than 5 days are not consistent with rabies infection (Tables 13.2, 13.3).

The gold standard for postmortem rabies diagnosis is the FAT, which was discussed earlier. In suspect cases, half the brain is submitted first for FA testing. On histopathology typical tissue "Negri bodies" can be found in the hippocampus; however,

Table 13.2. Phases of Rabies Infection in the Horse

Rabies infection	Phase 1	Phase 2	Phase 3
Also known as	Centripetal infection	CNS infection	Centrifugal infection
Duration	Incubation period: bite—first clinical signs: 2–9 weeks	Survival time (after first clinical signs): 5–10 days	Most of the infected horses will not reach this stage

Table 13.3. Clinical Signs of Rabies in Horses

Most Common Spinal Cord Form	Common Brainstem Form	Least Common Cerebral (furious) Form
(Ascending) paresis, paralysis	Dysphonia, dysphagia, pharyngeal paralysis	Aggressiveness
		Photophobia
		Hydrophobia
		Hyperesthesia
		Circling
	Head tilt	Roaring, teeth grinding
Loss of anal sphincter tone	Blindness	Convulsions
Loss of tail tone		
(Ascending) ataxia	Drooling	Depression

they are noticed in less than 50% of the FAT-positive cases. Spinal cord lesions are characterized by hemorrhage, perivascular cuffing, gray matter malacia, neuronophagia, and gliosis; however, none of these findings are specific to rabies.

Prevention

Vaccination is highly effective, but protection is not absolute. Vaccination of horses and of domestic virus reservoirs has been a very efficient way to lower the risk of virus transmission. Exposed and vaccinated horses may be revaccinated and quarantined for 45 days. However, it is recommended to euthanize the truly exposed (observed bitten by rabid animal) and unvaccinated horse.

Borna Virus—Bornaviridae

Characteristics: ARBO: unknown (not expected), enveloped: yes
Reservoir: shrews, possibly other rodents?
Endemic to: Central Europe (Mid and Southern Germany, Austria, Switzerland, and others?)

BDV causes a nonpurulent menigo-polioencephalitis which occurs in a very restricted geographical area of Central Europe and most commonly affects horses and sheep. Its name commemorates the city of Borna in Germany, where BD epidemics occurred in the 1890s. Presently, BD in horses is seen sporadically in the South of Germany, Switzerland, and Austria. However, there is ongoing and somewhat confusing discussion as well as contradictory information as to what species may also become infected, what the worldwide seroprevalence of BDV is, and whether there is a link to human seroprevalence and psychiatric disorders.

Epidemiology and Risk Factors

Clinical disease has a territorial restriction, seasonal peaks in spring and early summer, and varying incidence rates from year to year.[22,23] Clinical disease is described in limited endemic areas in Mid and Southern Germany, Switzerland, Liechtenstein, and Austria. BDV infections are more frequently found during January–June. Both horses and sheep can become affected. The disease incidence in previously endemic areas has decreased over decades. Seroprevalence among a variety of mammals including humans may be more widespread

including other areas of Europe, the Middle East, Japan, Australia, and the USA. Endemic areas have a higher seroprevalence in horses, and seroprevalence is greater than 50% on sites with a recent acute case among horses or sheep. BD may reoccur on locations any time from a few months up to several years. All information suggests a sylvatic, locally restricted virus reservoir and/or a vector.[22,24] A variety of rodent species can be infected experimentally and are under investigation as to their role of a natural virus reservoir. Very recently, the bicolored white-toothed shrew (*Crocidura leucodon*) has been identified as a potential BDV reservoir in an endemic area of BD in Switzerland.[25] It remains unclear how virus is transferred from the sylvatic host to the horse.

Pathogenesis

BDV penetrates the CNS in a fashion very similar to rabies virus—via retrograde axonal transport.[26] Virus is transported through the sensory tracts of the olfactory nerve with dendritic endings in the nasopharynx into the limbic system. From there, the virus spreads to most areas of the brain's gray matter with the exception of the cerebellum. The spinal cord is rarely affected.[23,27]

Clinical Signs

The incubation period, based on findings obtained from infection studies performed in the early 1920s, varies from 2 weeks to several months.[24] There is a fever in about 50% of the affected horses. BD can be peracute, acute, or subacute, and the mortality rate is usually greater than 80%. Some horses may survive; however, it is thought they remain persistently infected. BD usually presents with clinical signs consistent with infection of the cerebrum and limbic system. Altered behavior and repetitive motor activity such as circling, head pressing against objects, and chewing motions are seen. Fearfulness, changes to aggressive behavior, and compulsive behavior can be explained by involvement of the limbic system. Convulsions may be due to intracranial edema that develops during a later course of disease, and cranial nerve deficits may be observed during the later stages of infection.[23]

Diagnosis

BDV infection should be considered only in endemic areas, while other endemically relevant diseases should be ruled out. An infection with rabies virus is an important differential diagnosis; however, the spinal cord involvement is not typical of BD. A CSF sample frequently shows a mild-to-moderate mononuclear pleocytosis with an increased protein concentration due to intrathecal immunoglobulin production. An indirect immunofluorescence assay is advocated as the most reliable antigen-specific antibody testing. This test can be performed on both CSF and serum. However, because of an increased intrathecal production of antibodies when compared to serum antibody production, a BDV diagnosis can usually made faster analyzing CSF rather than serum.[23] Additional measurements of the AQ and IgG index are helpful with this diagnosis. For antigen detection, a reverse-transcriptase-PCR (RT-PCR) has been developed. Because this is a local/regional disease, the OIE does not have recommendations for testing, or reference laboratories.

Postmortem Examination

Histopathologic examination finds a nonspecific nonpurulent menigo-polioencephalitis. In less than 50% of the cases, cellular inclusion bodies (Joest–Degen bodies) can be found, and in particular in the hippocampus. Usually the diagnosis is made by immunohistochemistry, and alternatively antigen detection via *in situ* hybridization, Western blotting, or RT-PCR.

Clinical Course, Therapy, and Support

The clinical course and outcome are usually unfavorable. Horses deteriorate during the course of disease due to the development of intracranial edema. Specific treatments with amantadine sulfate, a virustatic drug, have not resulted in improvement or stabilization.[28] A very small number (single-digit percentage) of horses diagnosed with clinical BD are reported to have recovered spontaneously. Some horses show remission of clinical signs with a chance of chronic or recurrent disease.[24]

Prevention

There is currently no vaccine against BVD. Because several authors suggest rodents as a virus reservoir and vector, rodent control may help decreasing incidence of disease among horses. BDV with its envelope is probably very susceptible to detergents, desiccation, and UV radiation. Direct horizontal

transmission of virus from horse to horse has not been described, and quarantine measures of affected horses were not recommended by any of the cited authors. However, a study in sheep infected naturally with BDV showed evidence of a mononuclear cell-associated viremia based on RT-PCR results. In addition, RT-PCR-positive secretions from nose, conjunctiva, and saliva were found.[29] These findings provide evidence of subclinical infection, explain the increase in seroprevalence on affected premises, and make direct horse-to-horse transmission at least a possibility. Horses with clinical disease should therefore be quarantined from other horses or sheep, and isolation precautions should be instituted.[22–24,29]

ARBO VIRUSES ASSOCIATED WITH CENTRAL NERVOUS DISEASE IN HORSES

The ARBO viruses are a conglomerate of viruses belonging to different genera. They share a similar transmission mode: an arthropod vector. Virus replication usually also occurs in this vector. Many of the viruses discussed below are capable of causing disease in humans. In both horses and humans, viruses gain access to the blood stream causing a viremia for a limited number of days. In a small percentage of viremic horses or humans, the BBB is breached, and the virus causes an encephalitis/myelitis. The extent or site of neuropathy depends on the virus.

ARBO viruses which are capable of causing an encephalitis/myelitis in horses belong (worldwide) to three different genera: Togaviridae (Arbovirus group A), Flaviviridae (Arbovirus group B), and Bunyaviridae (Arbovirus group C).

EIAV is technically also an ARBO virus and can rarely cause neurologic disease in horses. Because it does not cause disease in humans, it is not included into the ARBO A, B, C grouping, and this viral disease will be discussed separately.

Togaviridae (Arbovirus Group A)

Eastern/Western/Venezuelan equine encephalitis viruses (EEE/WEE/VEE)
Characteristics: ARBO: yes; enveloped: yes
Endemic to: various parts of North, Central, and South America

These three viruses with the potential to cause encephalitis are so far geographically limited to the Americas. Due to a regular vaccination program with efficient vaccines against EEE and WEE, the disease incidence has been significantly decreased in North America. Each virus predominates in a specific geographical region; however, there is some overlap. EEE mainly occurs along the East Coast and in the Gulf Area of the United States; WEE predominates west of the Mississippi River, and VEE covers Central America and the Northern part of South America. EEE and VEE are genetically more closely related, and outbreaks of EEE and VEE have both been diagnosed in Argentina.

Epidemiology and Risk Factors

Bird species are the primary reservoir for all three viruses. Small rodents serve as an additional reservoir for VEE. Mosquitoes (Culex, Aedes, Anopheles, and Culiseta) transfer virus to horses and humans. Therefore, disease occurrence is linked to the summer season in temperate regions, and disease may be year-round in areas with (sub)tropical climate. Mammalian and bird species that were more recently introduced to the Americas are more likely to develop clinical signs of neuropathy while seroprevalence is widespread. The majority of infected susceptible animals or humans will become viremic with signs of fever, while only a small fraction will develop clinical CNS signs.[30] Horses and humans are considered dead-end hosts for EEE and WEE because the titer of viremia during infection is too low to induce infection of vectors. Unvaccinated horses are at risk to succumb to disease; however, they are neither directly nor indirectly contagious to one another. The titer of viremia in VEE-infected horses, on the other hand, may be high enough to infect vectors. In prevaccination times, outbreaks of equine encephalitis were common and characterized by high case fatality rates. Such outbreaks appear to be much reduced in recent years.

Pathogenesis

The horse is inoculated with the virus by an insect vector. Replication of virus begins in the subcutaneous tissue and muscle at the point of inoculation. Virus is then transported through lymphatics to the spleen and liver. A viremia follows which coincides with fever, depression, and anorexia. In a significantly smaller number of viremic horses, virus enters the CNS by crossing the BBB through endothelial cell penetration. This has been demonstrated for EEE and WEE; however, an experimental olfactorial route of CNS entry has been demonstrated for VEE.

CNS infection is mostly a gray matter cerebrocortical disease including cerebral cortices, thalamus, and hypothalamus, with milder and less frequent lesions toward caudal parts of the CNS. The brainstem and spinal cord are significantly less affected. Histological characteristics are neuronophagia, gliosis, and in severe cases malacia and necrosis of neuropil. Venules with swollen endothelial cells are common, with cuffed polymorphonucleated cells. A neutrophilic infiltration is typical of EEE, while VEE is characterized by a more mixed lymphocytic–neutrophilic infiltrate. WEE histology is usually more lymphocytic/plasmacytic rather than suppurative.[1] Histology and immunoperoxidase-staining techniques revealed virus in two confirmed EEE cases in cortex, thalamus, hypothalamus, and in a small number of affected neurons in brainstem and spinal cord, and absence of virus in the cerebellum.[31]

Clinical Signs

Encephalomyelitis is infrequently observed after infection. In experimental infections, 80–90% of the horses will become viremic and will develop a high fever. Only a fraction of horses will then develop clinical signs of encephalitis. Initial signs were hyperexcitability, which then develop into somnolence, depression, and recumbency. Cortical blindness, propulsive walking, head pressing, and ataxia are commonly encountered clinical signs.

Some affected horses that do not become recumbent may stabilize and survive. However, they may suffer permanently from cerebrocortical damage. A therapeutic plan should include antiinflammatory therapy (nonsteroidal preferred over corticosteroid treatments), DMSO, and excellent nursing care to avoid automutilation, decubital ulceration, and aspiration pneumonia. The prognosis for horses with signs of encephalitis is unfavorable. Death may occur after 5–14 days of rapid deterioration.

Diagnosis

Clinical signs are not pathognomonic. A bacterial meningoencephalitis, rabies encephalitis, or verminous encephalitis may cause similar clinical signs. It is very difficult to distinguish WNV infection from EEE and WEE, with both viral classes being endemic to the same areas. CSF may show a neutrophilic pleocytosis in particular with EEE cases. In addition to pleocytosis, there is usually an increase in CSF protein concentration.

Antigen-specific (IgM and IgG) antibody detection in serum or CSF is possible (visit http://www.oie.int recommendations). Clinical signs of encephalitis are usually preceded by viremia and fever, which allows the production of IgM and IgG. Seroconversion as determined by a four-fold increase in antibody titer may not be found if the first serum sample is taken when signs of encephalitis are present. The immunogenic stimulation may have been strong enough already for the production of immunoglobulins before the signs of encephalitis developed. Postmortem samples of brain can be used for virus culture, antigen, or specific antibody detection. Prevention is achieved through vaccination of horses and vector control (control of mosquito breeding areas).

Flaviviridae (Arbovirus Group B)

Japanese encephalitis (JE) virus, WNV, St. Louis encephalitis virus, Ilheus virus, Powassan virus, others

Characteristics: ARBO: yes; enveloped: yes

Endemic to: usually regional and geographically restricted

Members of Flaviviridae have the capacity to cause significant disease in a variety of mammals and in humans. There are several flaviviruses around the world which cause encephalitis in horses, and even more in humans. These viruses are known for their restricted geographical occurrence. St. Louis encephalitis virus and Powassan virus in the United States may be responsible for isolated cases of encephalitis in horses[32–34]; however, these viruses have been more of a concern among people than horses. Ilheus virus is a flavivirus causing equine encephalitis in South America.[35] JE virus (JEV) in Australasia and WNV in Northern Africa, the Middle East, and Northern and Central America both cover large geographical areas and therefore cause significant disease in both humans and horses each year.[36–39]

West Nile Virus

WNV is currently the best-known member of the flavivirus group because of its unprecedented appearance and spread in North America, which started in 1999. Prior to this date, WNV infection in humans and horses was restricted to African countries along the Nile river and to the Middle East (Israel, Jordan, and Syria) with occasional outbreaks of encephalitis

in horses in the Mediterranean basin.[40–43] Its rapid spread after the introduction into an immunologically naïve population of horses, birds, and people in the United States in 1999 caused significant disease and losses. However, it launched a significant research effort, which also intensified research on flaviviruses in general.

Epidemiology and Risk Factors

WNV primarily replicates in birds, and migratory birds in the Old and New World are virus reservoirs and an important factor in the spread of the disease. Localized outbreaks of WNV disease in horses close to resting places of migratory birds were described for decades.[43] It is yet unclear how WNV was introduced to North America. Mosquitoes (Culex) harbor, then transfer virus from the bird reservoir into a variety of species. Horses and humans, however, are most commonly affected. Season is a critical risk factor for WNV occurrence, which is intricately connected to the life cycle and activity level of the mosquito vector. Risk factors for WNV infection are therefore: (i) residence in an endemic area, (ii) season, (iii) outdoor activity, such as 24-h pasture access, (iv) vaccination status, and (v) mosquito-control programs.

Pathogenesis

Virus is transmitted from the vector during feeding on the horse. Virus replication occurs initially at the site of inoculation, followed by a viremia, which is of short duration. It is at this time that horses show clinical signs of an uncomplicated infection with WNV: fever, depression, and anorexia. In some horses, the virus enters the CNS, the exact mechanism of which is unknown. It is suspected that an initial endothelial infection occurs followed by translocation into the CNS. The virus then infects neurons at various sites of the CNS causing a diffuse or multifocal polioencephalomyelitis with lesions that actually increase in number from the diencephalon throughout the hindbrain including the spinal cord. This is different from infections with Togaviruses (EEE/WEE), where involvement of the spinal cord is less common.[44]

Clinical Signs

While other horses in the same environment may show clinical signs of an uncomplicated WNV infection, a small number of horses out of the group (sometimes only a single horse) may show signs of neurological disease. This neurological disease is usually accompanied by a fever. Initially, signs of muscle fasciculations of the entire body, particularly of the head and neck, are frequently described. Weakness, ataxia, and dysmetria are characteristics of this infection. Cranial nerve function can become affected, and mentation may be affected indirectly due to intracranial edema. Direct lesions to the cortex and cerebellum are rare.[44] These are important differences compared to a Togavirus infection.

Clinical Course, Therapy, and Support

Hyperimmune plasma as a specific treatment for WNV infections is available in the US, but its efficacy is not well documented.[45] There is no effective virustatic currently available, so supportive care is the only treatment option. The encephalomyelitis can be overwhelming and can cause sudden death in horses. Gait deficits can be very severe in some horses, while encephalitis and mentation changes may predominate in others. Therapy should aim at decreasing the amount of inflammation by administering nonsteroidal antiinflammatory drugs and by decreasing cerebral edema and spinal cord swelling by applying osmotic agents intravenously (mannitol and DMSO). The use of corticosteroids is controversial due to their immunosuppressive action, which potentially allows virus to propagate. However, a case report of human WNV claims that corticosteroid therapy was beneficial to a patient with flaccid paralysis due to a WNV infection[46] and has been frequently used by clinicians in the US. Based on empirical data, it is recommended to treat WNV-affected horses with corticosteroids (M. Furr, personal communication).

Diagnosis

A diagnosis is made easier when risk factors are taken into account. Caution has to be exercised that WNV infections are not overdiagnosed in endemic areas. In most cases, there is fever or a recent history of fever in combination with occurrence of clinical neurological disease. Muscle fasciculations of the face, the neck, or the entire body are frequently noticed during WNV infections.

A CBC usually reveals a lymphopenia, while a CSF sample shows a plasmacytic/lymphocytic pleocytosis in combination with an increased protein concentration. Antigen-specific testing is routinely

done indirectly by a WNV IgM capture ELISA (WNV-MAC), a plaque-reduction neutralization test (PRNT), or a WNV hemagglutination inhibition assay (WNV HI). Currently preferred is the WNV-MAC because it provides a positive result early during infection, and vaccination titers will not interfere with the interpretation of the test results. CSF and serum can be used for the WNV-MAC; however, at the onset of clinical neurological signs, the CSF-IgM concentration may be too low to measure, while there should already be a serum immunoglobulin response.

Brain material collected during a postmortem exam can be used for virus culture, and immunohistochemistry will correlate (histo)pathological lesions with antigen presence.

Prevention is primarily dependent upon vaccination of horses in endemic areas and vector control.

Japanese Encephalitis Virus

This virus is considered the Australasian equivalent to WNV. It has a vast geographical distribution extending from the southeastern Russian Federation, through India and Thailand to Japan. JE cases also occur in northeastern Australia, and similar to WNV horses and humans they can become infected.

Epidemiology and Risk Factors

The pig is the primary virus reservoir for JEV, with an extensive viremia without causing neuropathy. Birds, mainly egrets and herons, can also harbor virus. A growing pig industry in combination with cutting of forests and irrigation in Southeast Asia has increased the incidence of JEV infections. Both measures enlarged the habitat for the vector and the primary reservoir. Disease occurrence is year-round in tropical areas, and it is associated with the rainy season in subtropical and temperate regions. Similar to WNV, horses infected with JEV develop a low-grade viremia only, which makes a transmission from horse to horse difficult at best.

Pathogenesis and Clinical Signs

Many horses become febrile and viremic after the transmission of virus from the mosquito vector (Culex). The fraction of infected horses which will develop encephalitis is small. In contrary to WNV, myelitis is uncommon with clinical JE, and clinical signs of encephalitis predominate.

Fever is often present, associated with changes in mentation which range from somnolence to rage. Mild clinical neurological signs included neck rigidity, loss of coordination, staggering, and falling. Muscle fasciculations are common, which can be explained by affected motor nuclei. A documented outbreak of JE among a small group of horses described behavioral changes such as aimless wandering, ataxia, recumbence, death, and self-inflicted injury.[39]

Therapy is palliative and nonspecific. There is not much information available on residual postinfection neurologic deficits.

Diagnosis

Nonspecific diagnostics such as CSF changes with acute disease are not well documented. Antigen-specific diagnostics are available. These are antigen detection by PCR on plasma, CSF, and CNS tissue, or antigen by virus isolation on plasma during viremia, CSF when clinical signs are evident, and on CNS tissue during postmortem examination. Antibody detection is done with an IgM capture ELISA on serum, and immunohistochemistry can provide a definitive postmortem diagnosis.

Prevention

Control measures focus on vaccination, vector-control measures, and decreased vector exposure. Several vaccines are available; however, vaccination and boosters should be completed well before the season of peak mosquito activity.[39]

Powassan Virus

Epidemiology and Risk Factors

Powassan virus is a well-established cause of tick-born encephalitis in humans. The woodchuck and the snowshoe hare are the virus reservoir. The (ARBO) vectors are ticks from the genus *Dermatocentor*. Powassan virus strain M794 is long known to infect human and animals in Canada and was for a long time suspected to cause disease in horses. After intracerebral inoculation in rabbits and horses, the rabbits showed no clinical signs of encephalitis, but widespread histopathological changes were observed during necropsy. Eight days after inoculation in horses, significant neurological

signs occurred, and histopathological lesions were those of nonsuppurative encephalomyelitis, neuronal necrosis, and focal parenchymal necrosis.[34] However, Powassan virus has never been confirmed to cause significant equine disease, and it may be only an incidental finding.

Bunyaviridae (Arbovirus Group C)

Cache Valley virus, Maguari virus, Santa Rosa virus, California encephalitis virus, Jamestown Canyon virus, La Crosse virus, Melao virus, Snowshoe hare virus, Main Drain virus, Tacaiuma virus, and others

Characteristics: ARBO: yes; enveloped: yes

Endemic to: usually regional and geographically restricted

The group of Bunyaviridae contains a large number of encephalitis-causing viruses which are of primary concern in human medicine. Reports on infections in horses have been limited to studies on seroprevalence and case reports.[47,48] The concern is that with the spread of their natural vector and/or reservoir, they may form potential threats in the future. Members of Bunyaviridae that are (potentially) associated with encephalomyelitis in horses are the (i) Bunyamwera virus group: Cache Valley virus, Maguari virus, and Santa Rosa virus. These viruses are endemic to North, Central, and South America; (ii) the California encephalitis virus group: California encephalitis virus, Jamestown Canyon virus, La Crosse virus, Melao virus, and Snowshoe hare virus, which are endemic to North, Central, and South America; (iii) Main Drain virus (North America) and Tacaiuma virus (South America). Many more may exist in localized habitat and may form a future threat to a variety of species.

A variety of mammals and birds serve as virus reservoirs. A risk factor is certainly deforestation and cultivation of land, which includes irrigation. This potentially brings susceptible animals such as the horse (and people) in closer contact with the transmitting vector and the virus reservoir. Specific control measures are not determined.

VIRUSES THAT CAUSE A NEUROPATHY BY DAMAGING THE BBB

Equine herpesvirus

Equine infectious anemia virus

Equine Herpesvirus (1 and 4)—Alphaherpesviridae

Characteristics: Enveloped virus with the ability to induce a latent infection in the horse.

EHV-1 was detected as a cause of neurological disease to horses in the mid-1960s.[49] EHV-1 causes respiratory disease, abortion, and neonatal death with more frequency than it causes neuropathy. The very closely related EHV-4 virus has been incidentally isolated from aborted fetuses and from spinal cord lesions. Reports on EHV-4-associated myeloencephalopathy are extremely rare and so far have only been reported from continental Europe.[50] EHV myeloencephalopathy (EHM) usually occurs under outbreak conditions. The majority of horses develop a fever, and only a small fraction of horses develop neurologic signs.

Epidemiology and Risk Factors

EHM outbreaks occur more commonly during winter and early spring. Crowding of horses may be responsible for this higher incidence. Reports of EHM outbreaks are so far only available from the temperate areas of both hemispheres. EHM is less likely to occur in horses younger than 3 years of age, and in a variety of breeds comprising archetypical pony breeds (Shetland pony, Dartmoor pony, Fjord, Haflinger, Icelandic pony, potentially also the Friesian horse). Additional risk factors are barns that house horses with an extensive travel schedule or sales activities.[51] EHM occurs on unvaccinated and vaccinated premises, and newly affected horses are identified in small clusters. These clusters may occur in weekly intervals during a period of 4–6 weeks. A cluster can be only febrile horses, or horses with a fever and/or clinical signs of myeloencephalitis. Usually febrile horses outnumber neurologically affected horses by at least 2:1.

Pathogenesis

Virus transmission occurs from one virus-shedding horse to another by droplet infection. The shedding horse could be a horse where latent present virus is reactivated, or a horse that became horizontally infected from another horse. Virus enters the respiratory epithelium and is from there transported to regional lymph nodes. It enters peripheral blood mononucleated cells (PBMCs, monocytes, and lymphocytes) and subsequently circulates in the blood

stream. Because virus is located within a cell, this transport mechanism is referred to as a "cell-associated viremia." It is thought, however not demonstrated, that virus-carrying PBMCs make contact with the endothelium that supply the CNS and that virus crosses from PBMC into the endothelial cells. This results in a vasculitis with thrombosis in this particular vasculature which causes hypoxia and ischemia to the adjacent CNS tissue.[52] The combined effect of all "random hits" to the vasculature of the CNS relates to severity of clinical neurological disease. Because of the absence of a true infection of the nervous tissue, this disease is considered a neuropathy and not a neuritis, hence equine herpesvirus myeloencephalopathy (EHM).

Clinical Signs

EHM is typically a disease of the spinal cord. The midbrain, pons, and medulla (encephalopathy) are occasionally involved, however usually in combination with a myelopathy. Vasculopathies can occur at any level of the spinal cord and are seen in the gray and white matter alike. Ataxia, dysmetria, and weakness occur at varying degrees. The most feared presentation is a hind limb paralysis or a tetraparalysis. However, this severe form of EHM is found in only a small fraction of all neurologically affected horses during an outbreak. Most horses present with a mild-to-moderate ataxia affecting fore and hind limbs. Because the nervous tracts in the spinal cord connect the micturition center in the cortex with the urethral sphincter in the neck of the bladder, it is a long and very vulnerable tract for hypoxic-ischemic attacks. A spastic or upper motor neuron (UMN) bladder is therefore frequently seen in cases of EHM.

Diagnosis

EHM can be suspected when clinical signs of a myelopathy are recognized in more than one horse, and there are more febrile cases, or a history of recent febrile cases on the premise. Ideally, there is contact history of an index horse with other horses during competition, training, or sales.

Laboratory diagnosis is made by demonstrating the causative agent. Currently, this is done most quickly by showing EHV-1 DNA by PCR on nasopharyngeal swabs or in peripheral blood leukocytes (PBL). Febrile horses are usually the horses that are viremic, and by preference PBL should be collected during fever because of the increased chance to find viral DNA. Because of the large quantities of virus in nasal swabs, it is a good sample to submit to determine whether EHV is the cause of a disease outbreak. While viremia and fever are of short duration, the nasal shedding of virus is continuous for up to 14 days. Culture of viruses requires more time when compared to PCR, and the viral envelope may have been damaged by improper sample handling or long transportation, which will not allow the virus to grow in appropriate cell cultures. If virus is submitted for culture purposes, it is strongly recommended that samples be sent in virus transport medium.

CSF analysis shows very distinct changes characteristic of a vasculopathy: CSF cell count is normal (<5 WBC/ul), the total protein concentration is usually increased, the AQ is increased, and there is moderate-to-marked xanthochromia. EHV-1 (DNA)-specific PCR run on CSF is likely to be negative because DNA copy numbers are usually below detection limits. Be aware that EHV-1 antibodies in CSF during acute infection may be present due to leakage from the serum into the CSF containing spaces, and also can be found in CSF at low concentrations when there is a significant titer present in serum. Spinal cord lesions on histopathology are sometimes difficult to detect. It is recommended to make frequent cut sections into the formalin-fixed tissue. Small areas of hemorrhage can be a clue to proceed with histopathological investigation. Microscopic findings include a vasculitis with secondary injury to the neural parenchyma. Vascular thrombosis may be found, but there is a more profound vasculitis in the tunica adventitia and media. Pyknosis of endothelial cells and perivascular cuffing, predominantly with mononuclear cells, is found. Parenchymal injury ranges from infarcts to areas of less severe degeneration.[1] Viral antigen can be shown by immunohistochemistry.

Clinical Course, Therapy, and Support

Development of clinical signs is usually sudden, and preceded or accompanied by fever. Clinical signs can worsen during a 48-h period, after which gradual improvement occurs. Horses that become tetraplegic may recover; however, residual deficits can be observed. Mildly affected horses have a fair chance for recovery. With intensive nursing care, one should bear in mind that a tetraplegic horse is

still shedding large quantities of virus through its respiratory tract. Stringent isolation precautions should be taken to make sure virus is not transmitted to other horses.

Most clinically affected EHM horses eat and drink well. Their micturition ability should be monitored. In case where there is evidence of a spastic (or UMN) bladder, it is necessary to catheterize the bladder (aseptically) at least twice to three times daily. It is highly recommended to treat catheterized horses with a broad-spectrum antibiotic.[2] Lowering the virus load during viremia using acyclovir, a virustatic drug effective against herpes viruses, may be beneficial; however, it is probably essential that these drugs are applied during or preferably before viremia occurs. The effectiveness of acyclovir in horses with EHV is very questionable, however. Corticosteroids have been frequently advocated in the treatment of EHM. The advantages/disadvantages are already discussed in the introduction to this chapter. Empirically, this author has good experiences with once-daily aspirin administrations (acetylsalicylic acid: 6mg/kg once daily by mouth) as soon as a fever is detected during an outbreak of EHM. The drug may inhibit contact between the virus-carrying cell during viremia and the endothelial cell of the CNS, or it may interfere with a response pattern of the endothelial cell once infected.[51] Quarantine for the entire facility should occur and should persist for at least 3 weeks from the day that the last horse had a fever.

Prevention of neurologic disease due to EHV-1 is difficult. Immediate biosecurity and infection-control measures should be imposed on any suspect horse. Quarantine of new horses that come onto a premise is advisable. Numerous vaccines are available for EHV-1; while effective for the respiratory form of the illness, these products have not been shown to control neurologic disease due to EHV-1.

Equine Infectious Anemia Virus—Retroviridae, Nononcogenic Lentivirus

Characteristics: ARBO: yes; enveloped: yes

EIAV causes a multisystemic disease in horses (and all equidae) affecting all ages and breeds.[53] The disease is characterized by an immune-mediated (hemolytic) anemia. A persistent infection causes intermittent flare-ups of disease with fever, weight loss, anemia, and rarely ataxia. EIA virus is a vector-transmitted virus (Tabanidae: horse fly and deer fly); however, because of an intermittently occurring viremia, virus may also be transmitted mechanically or by blood transfusions.

The pathogenesis for ataxia or myelopathy caused by EIA virus is poorly understood, probably because of its rare occurrence. There is leptomeningeal inflammation, inflammation of the choroid plexi, and an ependymitis. Inflammation is most pronounced in the spinal cord. Involvement of the neural parenchyma is secondary to perivascular damage or to disruption of ependymal cells. Whether this is an immune-complex disease or due to invasion of virus-carrying macrophages breeching the BBB is not understood.[54]

Clinical Signs

Ataxia has been reported to be symmetrical, involving all four limbs. Positive serology (agar immunodiffusion test, or "Coggins' Test") will be present, and CSF may show a mild (lymphoplasmacytic) pleocytosis, increased protein concentration, and mild xanthochromia. Interestingly, the myelopathy does not necessarily coincide with the presence of anemia.

EIA-infected horses form a potential virus reservoir, and the use of corticosteroids, may cause recrudescence of virus. It is therefore advised to euthanize EIA-infected horses.

Prevention is achieved by elimination of carriers and vector control, regular testing of blood/plasma product donor herds, and aseptic injection and surgical technique to minimize iatrogenic infection.

CANDIDATE AND RARE VIRUSES FOR EQUINE NERVOUS SYSTEM DISEASE

Hendra and Nipah virus—Paramyxoviridae
Characteristics: ARBO: no; Enveloped: yes
Australia and Malaysia, Singapore
Zoonotic potential

Hendra (Australia) and Nipah (Singapore and Malaysia) Virus in Horses

When Hendra virus infections first occurred in Australia, it was feared that it would become a permanent threat to horses and to people in close contact with horses. Only two small-scale outbreaks are reported to date. The virus reservoir are flying foxes (a bat population, *Pteropus* spp.), and virus transmission occurs when there is close contact with

body fluids of these bats and is probably via inhaled aerosols.

Pathogenesis and Clinical Signs

This virus exhibits a strong preference for the respiratory endothelial cell, and horses during the Hendra virus outbreaks developed high fevers and severe respiratory distress because of a severe interstitial pneumonia. Fourteen horses died due to severe illness, and seven more seroconverted; however, those were euthanized to minimize further risk of transmission. None of these horses exhibited clinical neurological signs. Interestingly, in an infection experiment where 14 horses were infected, all 14 developed fulminate pulmonary disease. Seven horses had to be euthanized within 36 h because of the severity of disease. Of the seven remaining horses, two recovered, and they subsequently showed mild neurological signs indicating cortical disease. These two horses were also euthanized, and histology showed mild, multifocal lesions of a nonsuppurative encephalitis in the cortex.

Nipah virus is a close relative to Hendra virus, and it can cause neurological disease in humans. Its primary virus reservoir is currently unknown; however, it is likely to be fruit bats (*Pteropus* spp.) very similar to Hendra virus. Pigs can become infected, which will develop mild respiratory disease, and a single horse was diagnosed with Nipah encephalitis. However, seroprevalence in horses is more widespread, and the concern is that horses, pigs, and dogs form intermediate virus hosts which in turn may infect humans when in close contact.

Louping Ill virus (a flavivirus) has been the subject of one report of three horses in which muscle tremors, recumbency, and abnormal behavior were seen. Serologic evidence of infection was present, and Louping Ill virus was recovered from the CNS of one horse. In addition, meningoencephalitis caused by the pseudorabies virus (a herpes virus) has been reported and demonstrated to fulfill Kochs postulates in the horse.[55,56] Clinical signs of excessive sweating and mania were noted in a naturally affected horse, and severe clinical signs were described in two ponies infected with the virus.[56] Finally, a neurologic disease of high mortality with muscle tremors, ataxa, and lateral recumbency, termed Nigerian equine encephalitis, has been described.[57] The significance of these isolated infections is not known at this time.

REFERENCES

1. Summers BA, Cummings JF, DeLahunta A. 1995. *Veterinary Neuropathology*. St. Louis: Mosby. xiii, 527 p.
2. Goehring LS, Sloet van Oldruitenborgh-Oosterbaan MM. 2001. The mystery of equine herpes myeloencephalopathy. *Equine Vet Educ* 13: 36–42.
3. Steiner I, Budka H, Chaudhuri A, *et al*. 2005. Viral encephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol* 12: 331–43.
4. Furr MO, Tyler RD. 1990. Cerebrospinal fluid creatine kinase activity in horses with central nervous system disease: 69 cases (1984–1989). *J Am Vet Med Assoc* 197:245–8.
5. Chrisman CL. 1992. Cerebrospinal fluid analysis. *Vet Clin North Am Small Anim Pract* 22:781–810.
6. Pusterla N, Wilson WD, Conrad PA, *et al*. 2006. Comparative analysis of cytokine gene expression in cerebrospinal fluid of horses without neurologic signs or with selected neurologic disorders. *Am J Vet Res* 67:1433–7.
7. Porter MB, Long M, Gosche DG, *et al*. 2004. Immunoglobulin M-capture enzyme-linked immunosorbent assay testing of cerebrospinal fluid and serum from horses exposed to west Nile virus by vaccination or natural infection. *J Vet Intern Med* 18:866–70.
8. Lacombe VA, Podell M, Furr M, *et al*. 2001. Diagnostic validity of electroencephalography in equine intracranial disorders. *J Vet Intern Med* 15:385–93.
9. Sanders SG, Tucker RL, Bagley RS, *et al*. 2001. Magnetic resonance imaging features of equine nigropallidal encephalomalacia. *Vet Radiol Ultrasound* 42:291–6.
10. Ferrell EA, Gavin PR, Tucker RL, *et al*. 2002. Magnetic resonance for evaluation of neurologic disease in 12 horses. *Vet Radiol Ultrasound* 43:510–6.
11. Spoormakers TJ, Ensink JM, Goehring LS, *et al*. 2003. Brain abscesses as a metastatic manifestation of strangles: symptomatology and the use of magnetic resonance imaging as a diagnostic aid. *Equine Vet J* 35:146–51.
12. Verdegaal EJ, Kroeze EJ, Dik KJ, *et al*. 2003. [Unilateral facial paralysis and keratitis sicca, signs of temporohyoid osteoarthropathy in the horse]. *Tijdschr Diergeneeskd* 128:760–6.
13. Schultheiss PC, Collins JK, Hotaling SF. 1997. Immunohistochemical demonstration of equine herpesvirus-1 antigen in neurons and astrocytes of horses with acute paralysis. *Vet Pathol* 34:52–4.

14. Schmidt P, Meyer H, Hubert P, *et al*. 1994. In-situ hybridization for demonstration of equine herpesvirus type 1 DNA in paraffin wax-embedded tissues and its use in horses with disseminated necrotizing myeloencephalitis. *J Comp Pathol* 110:215–25.
15. Meyding-Lamade U, Oberlinner C, Seyfer S, *et al*. 2003. Experimental herpes simplex virus encephalitis: a combination therapy of acyclovir and glucocorticoids reduces long term magnetic resonance imaging abnormalities. *J Neurovirol* 6:118–25.
16. Thompson K, Blessing W, Wesselingh S. 2000. Herpes simplex replication and dissemination is not increased by corticosteroid treatment in a rat model of focal herpes encephalitis. *J Neurovirol* 6:25–32.
17. Goehring LS, Kessels BG, van Maanen C, *et al*. 2006. Evaluation of nephelometry for albumin measurement in serum and cerebrospinal fluid: experiences with an indwelling subarachnoidal catheter system for repetitive cerebrospinal fluid collection in horses. *J Vet Diagn Invest* 18:251–6.
18. Hudson LC, Weinstock D, Jordan T, *et al*. 1996. Clinical presentation of experimentally induced rabies in horses. *J Vet Med B* 43:277–85.
19. Hamir AN, Moser G, Rupprecht CE. 1992. A five year (1985–1989) retrospective study of equine neurological diseases with special reference to rabies. *J Comp Pathol* 106:411–21.
20. Green SL, Smith LL, Vernau W, *et al*. 1992. Rabies in horses: 21 cases (1970–1990). *J Am Vet Med Assoc* 200:1133–7.
21. Callan RJ, Van Metre DC. 2004. Viral diseases of the ruminant nervous system. *Vet Clin North Am Food Anim Pract* 20:327–62.
22. Durrwald R, Kolodziejek J, Muluneh A, *et al*. 2006. Epidemiological pattern of classical Borna disease and regional genetic clustering of Borna disease viruses point towards the existence of to-date unknown endemic reservoir host populations. *Microbes Infect* 8:917–29.
23. Grabner A, Fischer A. 1991. [Symptomatology and diagnosis of Borna encephalitis of horses. A case analysis of the last 13 years]. *Tierarztl Prax* 19:68–73.
24. Richt JA, Grabner A, Herzog S. 2000. Borna disease in horses. *Vet Clin North Am Equine Pract* 16:579–95.
25. Hilbe M, Herrsche R, Kolodziejek J, *et al*. 2006. Shrews as reservoir hosts of borna disease virus. *Emerg Infect Dis* 12:675–7.
26. Mori I, Nishiyama Y, Yokochi T, *et al*. 2005. Olfactory transmission of neurotropic viruses. *J Neurovirol* 11:129–37.
27. Gosztonyi G, Dietzschold B, Kao M, *et al*. 1993. Rabies and borna disease. A comparative pathogenetic study of two neurovirulent agents. *Lab Invest* 68:285–95.
28. Ludwig H, Bode L. 2000. Borna disease virus: new aspects on infection, disease, diagnosis and epidemiology. *Rev Sci Tech* 19:259–88.
29. Vahlenkamp TW, Konrath A, Weber M, *et al*. 2002. Persistence of Borna disease virus in naturally infected sheep. *J Virol* 76:9735–43.
30. Rico-Hesse R. 2000. Venezuelan equine encephalomyelitis. *Vet Clin North Am Equine Pract* 16:553–63.
31. Del Piero F, Wilkins PA, Dubovi EJ, *et al*. 2001. Clinical, pathologic, immunohistochemical, and virologic findings of eastern equine encephalomyelitis in two horses. *Vet Pathol* 38:451–6.
32. Nelson DM, Gardner IA, Chiles RF, *et al*. 2004. Prevalence of antibodies against Saint Louis encephalitis and Jamestown Canyon viruses in California horses. *Comp Immunol Microbiol Infect Dis* 27:209–15.
33. Keane DP, Little PB, Wilkie BN, *et al*. 1988. Agents of equine viral encephalomyelitis: correlation of serum and cerebrospinal fluid antibodies. *Can J Vet Res* 52:229–35.
34. Little PB, Thorsen J, Moore W, *et al*. 1985. Powassan viral encephalitis: a review and experimental studies in the horse and rabbit. *Vet Pathol* 22:500–7.
35. Iversson LB, Silva RA, da Rosa AP, *et al*. 1993. Circulation of eastern equine encephalitis, western equine encephalitis, Ilheus, Maguari and Tacaiuma viruses in equines of the Brazilian Pantanal, South America. *Rev Inst Med Trop Sao Paulo* 35:355–9.
36. Lam KH, Ellis TM, Williams DT, *et al*. 2005. Japanese encephalitis in a racing thoroughbred gelding in Hong Kong. *Vet Rec* 157:168–73.
37. McCormack JG, Allworth AM. 2002. Emerging viral infections in Australia. *Med J Aust* 177:45–9.
38. Endy TP, Nisalak A. 2002. Japanese encephalitis virus: ecology and epidemiology. *Curr Top Microbiol Immunol* 267:11–48.
39. Ellis PM, Daniels PW, Banks DJ. 2000. Japanese encephalitis. *Vet Clin North Am Equine Pract* 16: 565–78.
40. Autorino GL, Battisti A, Deubel V, *et al*. 2002. West Nile virus epidemic in horses, Tuscany region, Italy. *Emerg Infect Dis* 8:1372–8.
41. Durand JP, Simon F, Tolou H. 2004. [West Nile virus: in France again, in humans and horses]. *Rev Prat* 54:703–10.
42. Joubert L, Oudar J, Hannoun C, *et al*. 1970. [Epidemiology of the West Nile virus: study of a focus

in Camargue. IV. Meningo-encephalomyelitis of the horse]. *Ann Inst Pasteur (Paris)* 118:239–47.
43. Murgue B, Murri S, Zientara S, *et al*. 2001. West Nile outbreak in horses in southern France, 2000: the return after 35 years. *Emerg Infect Dis* 7:692–6.
44. Porter MB, Long MT, Getman LM, *et al*. 2003. West Nile virus encephalomyelitis in horses: 46 cases (2001). *J Am Vet Med Assoc* 222:1241–7.
45. Nout YS, Reed SM. 2005. Management and treatment of the recumbent horse. *Equine Vet Educ* 17:324–36.
46. Pyrgos V, Younus F. 2004. High-dose steroids in the management of acute flaccid paralysis due to West Nile virus infection. *Scand J Infect Dis* 36:509–12.
47. Emmons RW, Woodie JD, Laub RL, *et al*. 1983. Main Drain virus as a cause of equine encephalomyelitis. *J Am Vet Med Assoc* 183:555–8.
48. Lynch JA, Binnington BD, Artsob, H. 1985. California serogroup virus infection in a horse with encephalitis. *J Am Vet Med Assoc* 186:389.
49. Saxegaard F. 1966. Isolation and identification of equine rhinopneumonitis virus (equine abortion virus) from cases of abortion and paralysis. *Nord Med Vet* 18:504–12.
50. Benetka VBM, Högler S, Möstl K. 2002. EHV4-bedingter Abortus in einem österreichischen Pferdebestand mit respiratorischen und neurologischen Krankheitsfällen. *Tierarztl Umschau* 57: 464–71.
51. Goehring LS, van Winden SC, van Maanen C, *et al*. 2006. Equine herpesvirus type 1-associated myeloencephalopathy in The Netherlands: a four-year retrospective study (1999–2003). *J Vet Intern Med* 20:601–7.
52. Edington N, Bridges CG, Patel JR. 1986. Endothelial cell infection and thrombosis in paralysis caused by equid herpesvirus-1: equine stroke. *Arch Virol* 90:111–24.
53. Sellon DC. 1993. Equine infectious anemia. *Vet Clin North Am Equine Pract* 9:321–36.
54. McClure JJ, Lindsay WA, Taylor W, *et al*. 1982. Ataxia in four horses with equine infectious anemia. *J Am Vet Med Assoc* 180:279–83.
55. Ingh T. 1990. Aujeskys disease in a horse. *J Vet Med B* 37:532–8.
56. Kimman TG. 1991. Aujeskys disease in horses fulfills Kochs postulates. *Vet Rec* 128:103–6.
57. Adeyefa CA, Tomori O, Akpavie SO, *et al*. 1996. Clinical and pathological features of Nigerian equine encephalitis. *Vet Rec* 138:323–5.

14
Bacterial Infections of the Central Nervous System

Martin Furr

Bacterial infection of the equine central nervous system (CNS) is fairly uncommon, affecting approximately 2.5% of 450 horses with any type of neurologic disease in one survey.[1] If horses with peripheral neuropathies and laryngeal hemiplegia are excluded, then 3.4% of horses with CNS disease had bacterial meningitis.[1] In another report, 5.7% of horses with complications from a strangles outbreak had CNS involvement.[2] Bacterial meningitis appears to be more common among neonatal foals than adults. Bacterial meningitis was seen in 8–10% of neonatal foals in two different retrospective reports,[3,4] while an overall incidence of 13% was reported in another study of neonatal sepsis in 61 foals.[5] It is possible that these numbers underreport the true incidence of illness in either foals or adults, due to the difficulties of diagnosis, and the common lack of complete evaluations of the CNS at postmortem or clinically. It certainly appears, from a clinical perspective, that bacterial meningitis is being more commonly recognized in clinical patients. This is likely due to the increased recognition of CNS disease, as well as increased familiarity and comfort with diagnostic techniques such as cerebrospinal fluid (CSF) collection.

AGENTS

Infectious agents documented in CNS infections of horses vary. Infections in neonates are most commonly associated with the agents which result in bacterial septicemia. Hence, Gram-negative bacteria predominate. In a report of 61 foals with septicemia, *Escherichia coli*-mediated meningitis was most common, with meningitis seen in seven of 21 foals with *E. coli*-mediated septicemia. Meningitis was also noted in one of eight foals with septicemic salmonellosis.[5] In adult horses, streptococcal species appear to predominate,[2,6–8] although infections with a wide variety of other organisms have been reported, including *Actinomyces,*[9] *Actinobacillus,*[10,11] *Listeria,*[12] *E. coli,*[1] *Psuedomonas psuedomallei* (melioidosis),[13] and *Klebsiella* (Table 14.1).[14]

PATHOPHYSIOLOGY

In humans, the most common pathogens for bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitides*. These organisms colonize the mucosa of the nasopharynx, then cross into the bloodstream, eventually reaching the choroid plexus.[15] In *E. coli*-induced meningitis, it has been demonstrated that multiple factors are necessary for invasion of the CNS across the blood–brain barrier (BBB).[16] Specific factors necessary include a threshold level of bacteremia ($>10^3$ cfu/ml blood) and invasion of host brain microvascular endothelial cells (BMECs) utilizing specific surface proteins (OmpA, Ibe proteins, and cytotoxic necrotizing factor-1).[16] Interestingly, *E. coli* invasion and transcytosis of BMEC occur without damage to the BBB or endothelial cells.[17] Bacteria are then transported through the cell and into the CSF alive, with subsequent proliferation. Some *E. coli* strains (i.e., *E. coli* K1) can traverse the BMEC, but do not survive, suggesting that additional capsular factors are needed to preserve viability.[16] Other bacteria which are known to result in bacterial meningitis in humans (i.e., *Listeria monocytogenes,* group B Streptococcus) utilize different signaling mechanisms to achieve the same result and are less fully characterized. It is unknown if similar mechanisms exist for equine pathogens, but it is reasonable to assume that there are.

Table 14.1. Bacteria Reported to Cause CNS Infections in Horses

Streptococcus equi[6,18]
Streptococcus zooepidemicus [6,18]
Unidentified Gram-positive organism[6]
Klebsiella spp.[14,18]
Salmonella spp.[5,55]
Actinobacillus lignieresi[11]
Listeria monocytogenes[12]
Streptococcus suis[7]
Actinobacillus spp.[10]
Actinomyces spp.[9]
Staphyococcus spp.[19]
Sphingobacterium multivorum[19]
Actinobacillus equuli[19]
Escherichia coli[5,43]
Borrelia burgdorferi[56]
Pseudomonas aeruginosa[46]
Pseudomonas pseudomallei[13]
Rhodococcus equi[44]

In horses, a variety of mechanisms are incriminated in bacterial colonization of the CNS. Penetrating wounds with traumatic implantation of bacteria and/or contamination of tissues is one way and is seen in horses with fractures of the head.[1] Hematogenous implantation arising during bacteremia is commonly believed to be a major mechanism and as noted above requires a significant bacteremia. The observation that this is a common pathogenesis is supported by the distribution of the CNS lesions in many cases, as well as by the well-documented association of meningitis in horses with multiple extranervous system abscesses and endocarditis.[2,9,10] Smith and colleagues describe a search of records of two University hospitals as well as the Livestock Disease Diagnostic Center in Lexington Kentucky in which 16 of 21 horses over 1 year of age with bacterial meningitis had "systemic disease."[18] The nature of the systemic illness was not described.

Immunosuppression is presumed to play a role in predisposing a horse to bacterial spread. In humans, there is an increased risk of bacterial meningitis in people with HIV and cancer; hence, it is likely that similar factors are operative in horses. Foals, which have a higher incidence of bacterial meningitis than adult horses, may be immunosuppressed due to the presence of failure of passive transfer with suboptimal IgG levels, as well as bacteremia from a necrotic umbilicus. These may explain their greater risk for meningitis; however neonatal foals also have a greater incidence of bacteremia, known to be a prerequisite for bacterial meningitis, than adults. Hence, the importance of the immune factors is not truly known and has not been carefully examined. It seems intuitively correct that there is some role, however. Immunodeficiency in adults with bacterial meningitis has also been reported.[19] Three horses with bacterial meningitis were found to also have common variable immunodeficiency, which was considered to have a significant role in the infection.[19] Meningoencephalitis was also reported in an Arabian foal with combined immunodeficiency.[12] The presence of an "immature" BBB, with greater permeability to bacteria, has been postulated for foals.[20] The hypothesis that the BBB of immature animals is more easily colonized and traversed than adults has been tested in juvenile rats and humans, and it has been demonstrated that there is no difference in the ability of bacteria to colonize or traverse the BMEC of juvenile animals.[21] This hypothesis has not been evaluated in horses.

A further mechanism of CNS infection is by extension of suppurative infections of the head. While the dura mater is considered highly resistant to bacterial translocation, it is susceptible at the points of penetration of nerve trunks. Smith *et al.*[18] described seven cases of bacterial meningitis which were associated with infectious processes of the head. Four of the seven horses had sinusitis. Thrombophlebitis was observed in the vessels of the sinuses, and it was proposed that hematogenous dissemination of bacteria from vascular connections to the venous sinuses at the base of the skull occurred. This should result in basilar empyema and pituitary abscessation, which was seen in four horses from another report in which three animals had suppurative infections of the head.[22] Migration along the optic nerve was considered to have occurred in some of the horses,[18] and direct invasion through the thin bones of the sphenopalitine sinuses (following necrosis) may also occur.

Once bacteria gain access to the CNS or subarachnoid space (SAS), they are able to proliferate readily, due to the reduced endogenous and innate host response mechanisms present. As discussed in detail in Section 1, Chapter 3, the CSF has a low concentration of white blood cells (WBCs), immunoglobulins, and complement compared to serum. These are

critical components necessary for efficient phagocytosis and early nonspecific bacterial clearance.

Following bacterial entry and proliferation in the CNS/SAS, a critical event in the pathophysiology of bacterial meningitis is the subsequent inflammatory reaction which ensues. It is widely considered that many of the neurologic signs and sequelae of bacterial meningitis result from inflammatory-mediated damage to the CNS, rather than the direct effects of the bacteria themselves.[15,23–25] As such, it is important to realize that neurologic injury can progress even after the CNS has been sterilized by antibiotic therapy.[15]

Bacterial cell wall components induce meningeal inflammation by stimulating the production of inflammatory cytokines from microglia, astrocytes, monocytes, CSF leukocytes, and microglial cells.[15] The primary response is the production of tumor necrosis factor (TNF) and interleukin-1 (IL-1), which can appear within the CSF within 1 h after experimental inoculation of lipopolysacharide (LPS) in the CSF. The cytokines act synergistically to increase the permeability of the BBB, which results in vasogenic edema and protein transudation into the CSF. The exudation of proteinacious material and leukocytes obstructs the flow of CSF, with secondary interstitial edema. The presence of inflammatory cytokines also leads to increased leukocyte migration into the CSF. Neutrophil activation, with subsequent release of inflammatory proteins, leads to cytotoxic edema, cell injury, and death. Leukocyte release tissue-destructive enzymes, reactive oxygen species, and proteolytic enzymes.[23]

In early meningitis, there is an increase in cerebral blood flow, which is followed by decreased blood flow and a loss of cerebrovascular autoregulation. Presence of vasculitis contributes to decreased blood flow and can result in infarction and thrombosis. The combination of interstitial, vasogenic, and cytotoxic edema results in increased ICP, with further deleterious effects upon blood flow. Clinical signs result from a combination of cellular (neuronal) dysfunction due to inflammation, neuronal cell death, and increased ICP which are mediated by circulatory and inflammatory mediator events.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are responsible for tissue remodeling via degradation of extracellular matrix components.[23] MMPs have been demonstrated to be present in the CSF of human patients with bacterial meningitis, with higher concentrations associated with poorer outcomes.[26] Further, the MMPs have been demonstrated to disrupt the integrity of the BBB during both experimental and naturally occurring meningitis.[26,27]

Nitric oxide (NO) concentrations are elevated in human patients with naturally occurring bacterial meningitis as well as experimental induced meningitis.[23] The role of this compound in bacterial meningitis is not clearly understood at this time, but it is clear that inducible NO magnifies the production of various inflammatory mediators such as IL1-b and TNF, as well as decreasing meningitis-induced BBB damage.[28] Another significant oxidant is peroxynitrate. Surrogates for peroxynitrate are increased in the CSF of patients with bacterial meningitis,[29] and treatment with a peroxynitrate scavenger, uric acid, significantly attenuates meningeal inflammation.[23] Lipid peroxidation of membranes is an important part of brain injury, and peroxynitrates, as well as other pro-oxidant compounds, are important initiators of this event.

A second crucial effect of the cytokines is the activation of phospholipase A2 and stimulation of the Arachidonic Acid (AA) cascade, with subsequent production of prostaglandins and leukotrines.[30,31] Prostaglandin E2 is a predominate prostaglandin produced during bacterial neuroinflammation and has deleterious effects upon the BBB, leading to WBC pleocytosis and increased CSF protein concentrations.[32,33] In addition, it has been demonstrated that the prostaglandins interrupt cerebral autoregulation (Figure 14.1).[34]

CLINICAL SIGNS

Clinical signs and syndromes associated with bacterial infection of the CNS can vary widely, depending upon the neuroanatomic localization of the lesion or lesions. Abscesses lead to signs of a focal, space-occupying lesion, or signs can be multifocal or diffuse in meningitis. In neonatal foals, early signs include depression, disorientation, and loss of the suckle reflex. Recumbency and seizures usually follow fairly quickly. In adult horses, the clinical signs are more variable, ranging from ataxia to severe dementia, blindness, and seizures. Adult horses with cerebral abscesses demonstrated depression, blindness, ataxia, and decreased facial sensation and head tilt.[6,8,35] Diffuse meningitis, or multifocal infection, leads to more generalized signs of ataxia and depression perhaps including

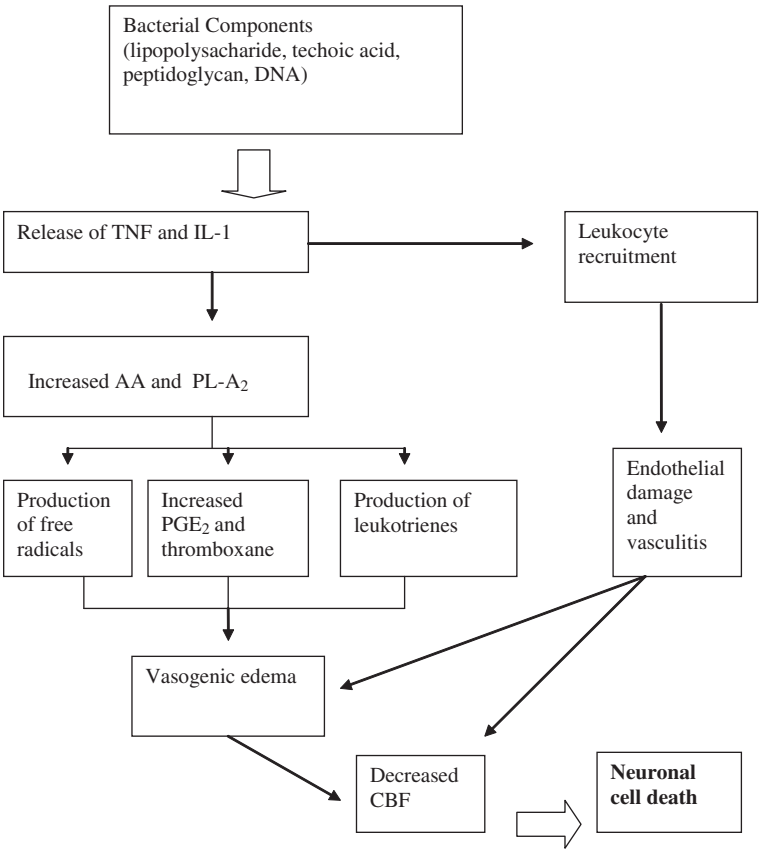


Figure 14.1. Mechanisms leading to brain injury in bacterial infections of the central nervous system.

cranial nerve signs. Papilledema may be present due to increased intracranial pressure.

DIAGNOSIS

Diagnosis of bacterial meningitis can be difficult, as clinical signs can be vague and nonspecific, as noted above. A history of a wound in the region of the head, or previous sinus infections, umbilical disease, or abscessing disease is suggestive. Additional signs of infectious disease, such as fever and increased WBC count and fibrinogen, are supportive, but not universally noted. In some reported and confirmed cases in adults, the horse had a normal peripheral WBC count.[6,35] Interpretation of the complete blood count (CBC) is more challenging and less definitive in neonatal foals, in which leucopenia associated with sepsis is very common.[3,36]

The most useful and definitive diagnostic test for bacterial meningitis is the CSF evaluation. Collection from either the atlanto-occipital (AO) or lumbosacral (LS) sites is acceptable, and the clinician should determine which site is preferred in the context of the entire clinical case. CSF should be collected early in the course of the disease, and submitted for a full examination, preferably before antibiotic therapy has begun. It has been demonstrated in human pediatric bacterial meningitis that pretreatment with antibiotics alters the clinical presentation and decreases the occurrence of positive results of the CSF culture.[37] In that report, pretreatment with antibiotics did not, however, alter CSF cell count and glucose or protein concentration.[37] Most commonly, the CSF will be turbid and discolored and will have an increased WBC count, which is predominately neutrophils, as well as an increased

CSF total protein. Total protein concentrations can range widely and are typically several hundred mg/dl, but cases have been reported with almost normal or very modestly increased total protein concentrations (98–121 mg/dl).[6,19,22] CSF nucleated cell counts can also vary widely, being normally grossly elevated, but sometimes only very modestly increased (17–22 cells/μl).[6,19] These very modest increases in CSF WBC make interpretation of the CSF difficult, as many horses have an increased CSF red blood cell (RBC) count, and the increased WBCs may be interpreted as due simply to blood contamination. Hence, modest increases in the CSF WBC or total protein should not be discounted; the prudent clinical course is to treat such cases as if bacterial meningitis is confirmed. Repeat CSF collection in such cases is warranted and may often demonstrate a more clear result (Table 14.2).

In horses, the CSF glucose concentration is reported to be from 35 to 77% of corresponding blood concentrations.[38] Decreased CSF glucose concentrations (hypoglycorrhachia) are often observed in bacterial meningitis, and values of "0" can be seen in humans.[15] This is presumed to be due to increased glucose consumption by neurons and infiltrating inflammatory cells. Bacteria may also utilize glucose but have been considered to be present in too small a number to play a significant role.[39] CSF glucose concentrations are rarely reported in the literature; however, in one series of two cases, the CSF glucose was normal.[35] Interpretation of CSF glucose concentrations in neonatal foals is quite problematic, as these patients are often hypoglycemic, but the CSF glucose/blood glucose should remain about 0.6 (normal). CSF lactate concentrations increase in bacterial meningitis;[40] however this appears to be a nonspecific increase and has little value in diagnosis of bacterial meningitis in humans.[41] Lactate has been reported to increase in horses with brain trauma, cerebral abscess, and eastern encephalitis[42] but has not been found to be of particular value in the diagnosis of bacterial meningitis.

CSF from any cases suspected of having bacterial meningitis should be cultured and an antibacterial sensitivity determined. The presence of bacteria as noted by cytologic evaluation of the CSF is strong supportive evidence, even in the absence of positive culture results.

Standard radiographs of the head or cervical spine are warranted if clinical examination and neuroanatomic localization dictates. Signs of osteomyelitis or trauma may be observed, but radiographs will be negative in many cases. Advanced imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), are becoming more available and are ideal modalities to confirm and provide precise localization of purulent intracranial or cervical disease. The diagnosis of brain abscesses by CT examination in living horses has been described and was used to guide therapy.[8,43,44] MRI of intracranial abscessation of horses has been described and appears to be a very useful diagnostic aid.[45,46]

Nuclear scintigraphy using labeled autologous WBCs can also be attempted and may provide definitive evidence (Figure 14.2).

TREATMENT

The objectives for the treatment of bacterial meningitis include (1) sterilization of the CNS/CSF, (2) control of inflammation, and (3) management of sequelae and complications.

The optimum antibacterial should be determined by culture and sensitivity testing of a CSF sample. However, antimicrobial treatment must begin before final culture results are determined. A Gram stain of CSF is valuable in making an empiric antimicrobial choice. Table 14.3 lists recommended antimicrobials for equine bacterial meningitis. Please refer to Section 1, Chapter 4, for a more thorough discussion of antibiotics for CNS infections. Chloramphenicol is a common choice, as it demonstrates a good spectrum of activity against many equine pathogens, and achieves good CSF concentrations. Enrofloxacin also achieves good concentrations within the CSF, but it has poor efficacy against streptococci and anaerobic bacteria and hence should not be used if these organisms are suspected.[47] Specific third-generation cephalosporins (cefotaxim, ceftazidime, cefepime, and ceftriaxone) are documented to achieve good CSF concentrations[48–50] and are good empiric choices, although expense may limit their use. Ceftiofur, a commonly used equine antimicrobial of the same class, has been shown not to enter the CSF, and its use in bacterial meningitis is not supported.[51] The "potentiated" sulphonamides (trimethoprim/sulfadiazine and ormetoprim/sulfadimethoxine) do achieve significant CSF concentrations after routine dosing; however, the presence of resistance to these drug

Table 14.2. Cerebrospinal Fluid Results in Some Reported Cases of Bacterial Infections of the Central Nervous System of Horses

Diagnosis	CSF Collection Site	Color/Clarity	WBC (Number/ µl)	RBC (Number/ µl)	Total Protein (mg/dl)	Culture	Comments
Brain abscess	AO	Not reported	Not reported	Not reported	98	*Streptococcus equi*	Died[6]
Brain abscess	LS	Xanthochromic	22	Not reported	300	*Streptococcus zooepidemicus*	Died[6]
Optic neuritis	LS	Cloudy	760	1590	93	*Actinobacillus* spp.	Died[10]
Meningitis	AO	Cloudy yellow	500	Not reported	170	No growth	Survived[35]
Meningitis	AO	Clear yellow	500		290	No growth	Survived[35]
Meningitis	Not reported	Cloudy yellow	>990	690	884	*Actinomyces* spp.	Died[9]
Cerebral abscess	AO	Xanthochromic	366000	Not reported	Not reported	*S. equi*	Survived, but later succumbed to laminitis[8]
Basilar empyema	AO	Cloudy yellow	31400	Not reported	84	Not reported	Died[22]
Basilar empyema	LS	Xanthochromic	11	770	119	Not reported	Died[22]
Meningitis	LS	Not reported	810	10	121	*Staphyococcus* spp.	Survived[19]
Meningitis	LS	Xanthochromic	17	Not reported	209	*Staphyococcus* spp. *Sphingobacterium multivorum*	Survived[19]
Meningitis	LS	Xanthochromic	223	Not reported	1600	No growth	Survived[19]

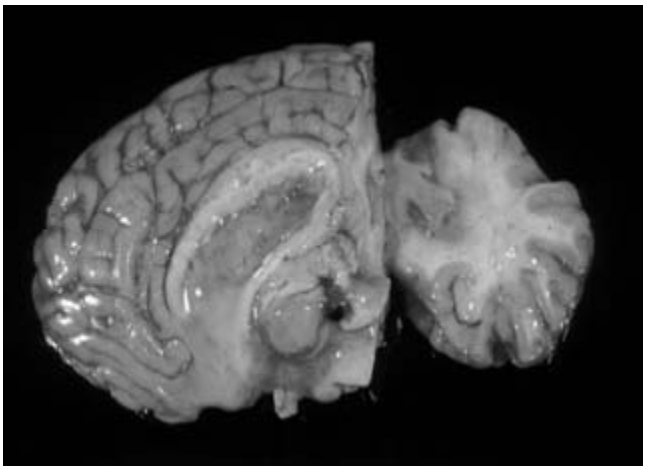


Figure 14.2. Suppurative ventriculitis in a foal.

combinations may make them less attractive, particularly if used empirically. Oxytetracycline, doxycycline, and the aminoglycosides do not achieve significant concentrations within the CSF and should not be used.

In cases of infection with resistant bacteria, intrathecal therapy can be considered. Anecdotal reports of seizures after the use of intrathecal penicillin exists; however, it is difficult to assess its validity. Aminoglycoside antibiotics are used in humans (intracerebroventricularly) and are described as well tolerated. Dosages of 5 mg are used, one per day in human adults.[52] Intraventricular vancomycin has also been used in humans at a dosage of 10–20 mg per day.[52] These treatments should be combined with systemic administration of the antibiotic.

The duration of treatment with antibiotics in horses with bacterial meningitis is difficult to assess. A total treatment duration of at least 3 weeks is advisable. Specific guidelines do not exist for the horse, but continuing treatment for at least 10 days beyond the resolution of clinical signs is advisable, as recrudescence has been noted in human patients. Repeat CSF analysis is indicated after antimicrobial treatment has been discontinued. In cases of cerebral abscess, longer treatment times are probably indicated, and follow-up CT or MRI studies are warranted to ensure resolution of the infection.

Neuroinflammation should be controlled aggressively to minimize the development of increased ICP, potential brain herniation, or exacerbation of clinical signs. The use of corticosteroids is controversial; however, a number of large-scale analyses have demonstrated that the use of dexamethasone in humans with bacterial meningitis is associated with a decreased risk of mortality and serious neurologic sequelae.[53,54] The risk of laminitis is of particular concern in horses, however, and corticosteroids should be used for as short a period of time as possible to minimize this concern. Nonsteroidal antiinflammatory drugs should be employed to minimize edema associated with inflammation. Intravenous dimethyl sulfoxide (DMSO) (0.5–1 g/kg IV, q 12–24 h) is widely used as an antiinflammatory drug and is commonly used by the author for neuroinflammation for the first 3 days of treatment. Other means of minimizing inflammation, such as MMP inhibitors and peroxynitrate scavengers (such as uric acid), show promise, but currently remain research tools only.[23]

Focal cerebral abscessation has been successfully treated surgically in several cases; however, CT or MRI localization appears to be important in planning surgery.[43,44] One mare was successfully treated and was recovering from the neurologic disease; however the horse developed laminitis which necessitated its destruction after about 2 months.[8] Surgical drainage via craniotomy and aspiration of the abscess appears to be a viable modality in the horse.

Ancillary treatments are determined by the specific needs of each individual patient. Horses that cannot eat or drink will require nutritional support and fluids, either provided via a nasogastric tube or

Table 14.3. Recommended Antimicrobials for the Treatment of Equine Bacterial Meningitis

Drug	Dose	Comments
Ceftazidime	50 mg/kg IV q 6 h	Extrapolated from human dose
Cefotaxime[49]	40 mg/kg IV q 4–6 h	
Cefepime[48]	11 mg/kg IV q 8 h	Kinetics determined in neonatal foals
Ceftriaxone[50]	50 mg/kg IV	
Chloramphenicol[57]	25–50 mg/kg PO	
TMS/SMZ[58]	2.4/12.5 mg/kg PO	Use only with appropriate documented sensitivity
OMP/SDM[59]	9.2/45.8 mg/kg (loading) 4.6/22.9 mg/kg PO q 24 h (maintenance)	
Enrofloxacin[60]	5.5 mg/kg IV q 24 h 7.5 mg/kg PO q 24 h	Significant arthropathy in foals
Rifampin[61]	10 mg/kg PO q 12 h	Must be used in combination due to resistance
Metronidazole[62]	15–25 mg/kg PO q 6 h	Limited spectrum to anaerobes

intravenously. Horses with seizures require anticonvulsant medication and associated care. Cranial nerve deficits may lead to failure to blink, resulting in corneal trauma. This can be managed with such compounds as artificial tears, or by performing a tarsorrhaphy. Depression may lead to a low head carriage, with secondary dependent edema of the head. If infections of the head are present, they will need appropriate care. Horses that are recumbent need to be managed to minimize trauma.

REFERENCES

1. Tyler CM, Davis RE, Begg AP, *et al*. 1993. A survey of neurological diseases in horses. *Aust Vet J* 70:445–9.
2. Sweeney CR, Benson CE, Whitlock RH, *et al*. 1987. *Streptococcus equi* infection in horses – Part II. *Compend Contin Educ Pract Vet* 9:845–51.
3. Koterba AM, Brewer BD, Tarplee FA. 1984. Clinical and clinicopathological characteristics of the septicemic neonatal foal: review of 38 cases. *Equine Vet J* 16:376–82.
4. Brewer BD, Koterba AM. 1990. Bacterial isolates and susceptibility patterns in foals in a neonatal intensive care unit. *Compend Contin Educ Pract Vet* 12:1773–81.
5. Platt H. 1973. Septicaemia in the foal. A review of 61 cases. *Br Vet J* 129:221–9.
6. Raphel C. 1982. Brain abscess in three horses. *J Am Vet Med Assoc* 180:874–7.
7. Devriese LA, Sustronck B, Maenhout T, *et al*. 1990. *Streptococcus suis* meningitis in a horse. *Vet Rec* 127:68.
8. Allen JR, Barbee DD, Boulton CR, *et al*. 1987. Brain abscess in a horse: diagnosis by computed tomography and successful surgical treatment. *Equine Vet J* 19:552–5.
9. Rumbaugh GE. 1977. Disseminated septic meningitis in a mare. *J Am Vet Med Assoc* 171:452–4.
10. Hatfield CE, Rebhun WC, Dietz AE, *et al*. 1987. Endocarditis and optic neuritis in a quarter horse mare. *Compend Contin Educ Pract Vet* 9:451–4.
11. Chladek DW, Ruth GR. 1976. Isolation of *Actinobacillus lignieresi* from an epidural abscess in a horse with progressive paralysis. *J Am Vet Med Assoc* 168:64–6.
12. Clark EG, Turner AS, Boysen BG, *et al*. 1978. Listeriosis in an Arabian foal with combined immunodeficiency. *J Am Vet Med Assoc* 172:363–6.
13. Ladds PW, Thomas AD, Pott B. 1981. Meliodosis with acute meningoencephalomyelitis in a horse. *Aust Vet J* 57:36–8.
14. Timoney PJ, McArdle JF, Bryne MJ. 1983. Abortion and meningitis in a Thoroughbred mare associated with *Klebsiella pneumoniae*, type 1. *Equine Vet J* 15:64–5.
15. Roos KL, Tyler KL. Meningitis, encephalitis, brain abscess, and empyema. In *Harrison's Principles of Internal Medicine*, edited by Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, 2471–90. New York: McGraw Medical.

16. Kim KS. 2002. Strategy of *Escherichia coli* for crossing the blood–brain barrier. *J Infect Dis* 186(Suppl. 2):S220–4.
17. Stins MF, Badger JL, Kim KS. 2001. Bacterial invasion and transcytosis in transfected human brain microvascular endothelial cells. *Microb Pathog* 30:19–28.
18. Smith JJ, Provost PJ, Paradis MR. 2004. Bacterial meningitis and brain abscesses secondary to infectious disease processes involving the head in horses: seven cases (1980–2001). *J Am Vet Med Assoc* 224:739–42.
19. Pellegrini-Masini A, Bentz AI, Johns IC, *et al*. 2005. Common variable immunodeficiency in three horses with presumptive bacterial meningitis. *J Am Vet Med Assoc* 227:114–22.
20. Santschi EM, Foreman JH. 1989. Equine bacterial meningitis – Part 1. *Compend Contin Educ Pract Vet* 11:479–83.
21. Stins MF, Nemani PV, Wass C, *et al*. 1999. *Escherichia coli* binding to and invasion of brain microvascular endothelial cells derived from humans and rats of different ages. *Infect Immun* 67:5522–5.
22. Reilly L, Habecker P, Beech J, *et al*. 1994. Pituitary abscess and basilar empyema in 4 horses. *Equine Vet J* 26:424–6.
23. Scheld WM, Koedel U, Nathan B, *et al*. 2002. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. *J Infect Dis* 186(Suppl 2):S225–33.
24. Tauber MG, Borschberg U, Sande MA. 1988. Influence of granulocytes on brain edema, intracranial pressure, and cerebrospinal fluid concentrations of lactate and protein in experimental meningitis. *J Infect Dis* 157:456–64.
25. van Furth AM, Roord JJ, van Furth R. 1996. Roles of proinflammatory and anti-inflammatory cytokines in pathophysiology of bacterial meningitis and effect of adjunctive therapy. *Infect Immun* 64:4883–90.
26. Leppert D, Grygar C, Miller KM, *et al*. 2000. Matrix metalloproteinase (MMP)-8 and MMP-9 in cerebrospinal fluid during bacterial meningitis: association with blood-brain barrier damage and neurological sequelae. *Clin Infect Dis* 31:80–4.
27. Lukes A, Mun-Bryce S, Lukes M, *et al*. 1999. Extracellular matrix degradation by metalloproteinases and central nervous system diseases. *Mol Neurobiol* 19:267–84.
28. Winkler F, Koedel U, Kastenbauer S, *et al*. 2001. Differential expression of nitric oxide synthases in bacterial meningitis: a role of the inducible isoform for blood–brain barrier breakdown. *J Infect Dis* 183:1749–59.
29. Kastenbauer S, Koedel U, Becker BF, *et al*. 2002. Oxidative stress in bacterial meningitis in humans. *Neurology* 58:186–91.
30. de Vries HE, Kuiper J, de Boer AG, *et al*. 1997. The blood–brain barrier in neuroinflammatory diseases. *Pharmacol Rev* 49:143–55.
31. Misko TP, Trotter JL, Cross AH. 1995. Mediation of inflammation by encephalitogenic cells: interferon gamma induction of nitric oxide synthase and cyclooxygenase 2. *J Neuroimmunol* 61:195–204.
32. Kadurugamuwa JL, Hengstler B, Bray MA, *et al*. 1989. Inhibition of complement-factor-5a-induced inflammatory reactions by prostaglandin E2 in experimental meningitis. *J Infect Dis* 160:715–9.
33. McGeer PL, McGeer EG. 1995. The inflammatory response system of the brain: implication for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res Rev* 21:195–218.
34. Mertineit C, Samlalsingh-Parker J, Glibetic M, *et al*. 2000. Nitric oxide, prostaglandins, and impaired cerebral blood flow autoregulation in group B streptococcal neonatal meningitis. *Can J Physiol Pharmacol* 78:217–27.
35. Newton SA. 1998. Suspected bacterial meningoencephalitis in two adult horses. *Vet Rec* 142:665–9.
36. Morris DD, Rutkowski J, Kent Lloyd KC. 1987. Therapy in two cases of neonatal foal septicemia and meningitis with cefotaxime. *Equine Vet J* 19:151–4.
37. Rothrock SG, Green SM, Wren J, *et al*. 1992. Pediatric bacterial meningitis: is prior antibiotic therapy associated with an altered clinical presentation? *Ann Emerg Med* 21:146–52.
38. Mayhew IG, Whitlock RH, Tasker JB. 1977. Equine cerebrospinal fluid: reference values of normal horses. *Am J Vet Res* 38:1271–4.
39. Baltch A, Osborne W. 1957. Inquiry into causes of lowered spinal fluid sugar content: *in vivo* and *in vitro* observations. *J Lab Clin Med* 49:882–9.
40. Knight JA, Dudek SM, Haymond RE. 1981. Early (Chemical) diagnosis of bacterial meningitis – cerebrospinal fluid glucose, lactate, and lactate dehydrogenase compared. *Clin Chem* 27:1431–4.
41. Jordan GW, Statland B, Halsted C. 1983. CSF lactate in disease of the CNS. *Arch Intern Med* 143:85–7.
42. Green EM, Green SL. 1990. Cerebrospinal fluid lactic acid concentrations: reference values and diagnostic implications of abnormal concentrations in adult horses. *Proc 18th Annual Meeting ACVIM* 18:495–9.
43. Cornelisse CJ, Schott HC, Lowrie CT, *et al*. 2001. Successful treatment of intracranial abscesses in 2 horses. *J Vet Intern Med* 15:494–500.

44. Janicek JC, Kramer J, Coates JR, *et al*. 2006. Intracranial abscess caused by *Rhodococcus equi* infection in a foal. *J Am Vet Med Assoc* 228:251–3.
45. Spoormakers TJP, Ensink JM, Goehring LS, *et al*. 2003. Brain abscess as a metastatic manifestation of strangles: symptomatology and the use of magnetic resonance imaging as a diagnostic aid. *Equine Vet J* 35:146–51.
46. Audigie F, Tapprest J, George C, *et al*. 2004. Magnetic resonance imaging of a brain abscess in a 10-month-old filly. *Vet Radiol* 45:210–5.
47. Dowling PM. 1999. Clinical pharmacology of nervous system disease. *Vet Clin North Am Equine Pract* 15:575–88.
48. Gardner SY, Papich MG. 2001. Comparison of cefepime pharmacokinetics in neonatal foals and adult dogs. *J Vet Pharmacol Ther* 24:187–92.
49. Gardner SY, Sweeney RW, Divers TJ. 1993. Pharmacokinetics of cefotaxime in neonatal pony foals. *Am J Vet Res* 54:576–9.
50. Ringger NC, Brown MP, Kohlep SJ, *et al*. 1998. Pharmacokinetics of ceftriaxone in neonatal foals. *Equine Vet J* 30:163–5.
51. Cervantes CC, Brown MP, Gronwall R, *et al*. 1993. Pharmacokinetics and concentrations of ceftiofur sodium in body fluids and endometrium after repeated intramuscular injections in mares. *Am J Vet Res* 54:573–5.
52. Nau R, Sorge F, Prange H. 1998. Pharmacokinetic optimisation of the treatment of bacterial central nervous system infections. *Clin Pharmacokinet* 35:223–46.
53. de Gans J, van de Beek D. 2002. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 347:1549–56.
54. Lebel MH, Freij BJ, Syrogiannopoulos GA, *et al*. 1988. Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. *N Engl J Med* 319:964–71.
55. Stewart BP, Martin BR, Williams LP, *et al*. 1973. Salmonella-induced meningoencephalitis in a foal. *J Am Vet Med Assoc* 162:211–3.
56. Burgess EC, Mattison M. 1987. Encephalitis associated with *Borrelia burgdorferi* infection in a horse. *J Am Vet Med Assoc* 191:1457–8.
57. Gronwall R, Brown MP, Merritt AM, *et al*. 1986. Body fluid concentrations and pharmacokinetics of chloramphenicol given to mares intravenously or by repeated gavage. *Am J Vet Res* 47:2591–5.
58. Brown MP, Gronwall R, Castro L. 1988. Pharmacokinetics and body fluid and endometrial concentrations of trimethoprim-sulfamethoxazole in mares. *Am J Vet Res* 49:918–22.
59. Brown MP, Gronwall RR, Houston AE. 1989. Pharmacokinetics and body fluid and endometrial concentrations of ormetoprim-sulfadimethoxine in mares. *Can J Vet Res* 53:12–6.
60. Giguere S, Sweeney RW, Belanger M. 1996. Pharmacokinetics of enrofloxacin in adult horses and concentration of the drug in serum, body fluids, and endometrial tissues after repeated intragastrically administered doses. *Am J Vet Res* 57:1025–30.
61. Kohn CW, Sams R, Kowalski JJ, *et al*. 1993. Pharmacokinetics of single intravenous and single and multiple dose oral administration of rifampin in mares. *J Vet Pharmacol Ther* 16:119–31.
62. Sweeney RW, Sweeney CR, Soma LR, *et al*. 1986. Pharmacokinetics of metronidazole given to horses in intravenous and oral routes. *Am J Vet Res* 47:1726–9.

15
Equine Protozoal Myeloencephalitis

Martin Furr

Equine protozoal myeloencephalitis (EPM) is a commonly diagnosed condition of the horse which was originally described in 1964 by J. Rooney and termed "segmental myelitis." Later descriptions used the terminology "focal myelitis encephalitis" or "toxoplasma-like encephalitis" when protozoan parasites were found in the central nervous system (CNS) of ataxic horses.[1,2] The observed organism was determined to be a member of the genus *Sarcocystis* in 1976, and an organism was cultured from an affected horse in 1991 and named *Sarcocystis neurona*, due to its association with neurons.[3,4] Since that time, the organism has been cultured from several other ataxic horses, and a variety of strains of the parasite have been described.[5–9] In addition, *S. neurona* or an *S. neurona*-like organism has been cultured from the CNS of a number of other species including the zebra,[10] domestic cat,[11] Canadian lynx,[12] sea otter,[13,14] straw-necked ibis,[15] mink, raccoon, and skunk.[16–18]

Experimental inoculation of horses with *S. neurona* has been shown to induce a syndrome of neurologic disease consistent with field cases, and it is clear that *S. neurona* is the major cause of the disease referred to as EPM.[19–22] In addition to *S. neurona*, however, the protozoan parasite *Neospora hughesi* and *N. caninum* have been recovered from a small number of horses with EPM-like illness, and they must also be considered a cause of EPM, although uncommon.[23,24] Toxoplasma has also been reported as a cause of EPM;[25] however, others have suggested that the organisms were misidentified and were truly *S. neurona*.[26]

EPIDEMIOLOGY

EPM is a disease of the American continent. Most horses with a diagnosis of EPM outside this region appear to have spent some time in the endemic area; however there are a few reports of neurologic horses with consistent clinical signs, positive Western blot (WB) test results, and no history of travel in the American continent.[27,28] The nature of the infection in these horses is unclear and may be due to cross-reacting antigens. Horses in the United States have a variable, but generally high serologic positive incidence to *S. neurona*, ranging from 10% among wild mustangs in Utah, 22% in the arid regions of Oregon, 45% in Pennsylvania, 53% in Ohio, and 60% in Michigan.[29–33] The seroprevalence for *N. hughesi* is generally low and varies with the method of assay. Using an indirect immunofluorescence assay and a titer of 1:100 as the cut-off, there is a seroprevalence of 37% in California, 20% in Montana, and 5% in New Zealand.[34] In another study of horses in California, the *N. hughesi*-seropositive rate was 1.7%/year of age.[35]

All horses are susceptible to the development of EPM, but epidemiological surveys have suggested that the average age of affected horses is 4.4 years in one study[36] and 3.6 years in another report.[37] The age range of reported cases is from 2 months[38] to 24 years.[39] Standardbreds and Thoroughbred horses have been reported to be overrepresented in some studies;[36, 40] however this is not consistent and may reflect selection bias. Horses of all breeds appear to be affected, and there is no gender bias. Most cases appear to be individual cases and "outbreaks" of EPM do not appear to occur.

Despite the often high rate of exposure to the organism, however, only a small percentage (perhaps $<1\%$) of horses develop clinical illness.[41] This suggests that immune clearance of the parasite is

very effective, but that unknown factors must exist in certain cases to allow clinical disease to be expressed. Parasite dose is likely to be a factor, and in fact this has been experimentally demonstrated.[20] Strain-related variance in virulence may also be involved, although this has not been examined critically. Other factors that have been considered to have a role in the induction of EPM include physiologic stress associated with shipping, training, showing, and pregnancy which may make animals more susceptible to EPM.[42] Indeed, one reliable model of inducing EPM incorporates long-range shipping as a stressor, performed immediately prior to infection.[43] Other attempts to induce EPM using the oral infection route and that do not incorporate stressors such as shipping, have led to inconsistent and only mild illness.[19] It is assumed that these stressors lead to some degree of immune suppression, which is a commonly implicated factor in protozoan parasite infections. However, treatment of horses with immunosuppressive doses of steroids associated with oral infection with *S. neurona* did not result in significantly worse histopathologic changes in the CNS, although clinical signs were slightly more severe than in nonsteroid-treated horses.[19] Additional evidence for the role of physiologic stress is found in the observation that stressed horses develop more severe clinical signs than naturally infected (nonstressed) horses.[44] It thus appears likely that stress has a role in the development of EPM; however, the interaction is complex and not fully understood at this time.

The life cycle of *S. neurona* remained confusing and incompletely understood for many years. Part of the confusion was a result of misclassification of the organism, and the belief that *S. neurona* and *S. falcatula* were the same organism. Subsequent work has confirmed that *S. neurona* and *S. falcatula* are indeed two distinct organisms. There are also other *Sarcocystis* species carried by the opossum which added complexity to the research efforts. Recent work from various laboratories has filled in many of the missing pieces of the life-cycle puzzle. *S neurona* is a typical coccidian parasite, in that it has a two-host life cycle. During part of the parasite life, it resides in one host, referred to as the definitive host, while during another phase of its life cycle it resides in the tissues of a second animal, known as the intermediate host. Sexual reproduction occurs in the definitive host, while asexual reproduction (i.e., growth and replication) occurs in the intermediate host. It has been known for many years that the definitive host for *S. neurona* was the opossum. This has been supported by numerous feeding studies, examination of feral opossums, and molecular studies in this species. Further, the clinical disease of EPM is found to coincide with the environmental range of the opossum. The identification of the intermediate hosts has remained much more challenging, however. It was originally considered that various species of birds were intermediate hosts; however this was based on improper identification of the organism residing in those species. Recent studies from several laboratories have identified the intermediate hosts to be the raccoon, skunk, and armadillo. Horses become infected by consuming the infective sporocyst which has been shed by the opossum into the environment. The horse has been considered to be a dead-end host and unable to transmit the disease to other horses, or in fact support the completion of the life cycle of the organism. This position has been challenged recently, however as mature shizonts and sarcocysts have been documented in a 4-month-old foal with clinical signs of EPM.[45] Further work is required to corroborate this finding.

PATHOPHYSIOLOGY

The pathophysiology of EPM is poorly understood, yet significant advances have been made in recent years utilizing genetically modified mice strains, newly developed infection models, and molecular techniques. Significant deficiencies remain, however.

During the normal life cycle of *S. neurona*, sporocysts are passed in the feces of the opossum, contaminating feed and water, which are then ingested by the intermediate host. Once within the gastrointestinal (GI) tract, the sporocysts excyst and release eight sporozoites which penetrate the gut and enter arterial endothelial cells in various organs. Meronts develop with the host cells, which then rupture and release merozoites into the blood stream. In the appropriate intermediate host, sarcocysts form in various muscle tissues. Once the intermediate host dies, the flesh is consumed by the definitive host, completing the life cycle.[41]

The development of *S. neurona* has been carefully examined in immunodeficient mouse strains, in which there is a gut phase, with sporozoites found in the small intestinal villi as well as the Peyer's patches within hours of inoculation. By 1 day after inoculation, organisms could be found in the mesenteric

lymph nodes and pancreas. A parasitemia was observed on days 1–8 after infection, and organisms were found in numerous tissues by 1 week after infection. Parasite was found in brain by day 5 after infection.[41] Thus, in immunodeficient mice, it appears that there is a hematogenous distribution of parasite occurring rapidly and with widespread seeding of tissues. The development of the parasite in immunocompetent horses has not been similarly examined; however, parasitemia in immunodeficient horses has been demonstrated,[46] and a transient parasitemia has been reported in one immunocompetent horse following oral challenge with *S. neurona*.[47]

The mechanism by which parasite enters the CNS is unknown; however, one attractive hypothesis is that the organism infects lymphocytes, which then carry the organism to the CNS during tissue surveillance.[48] This hypothesis is supported by the observation that leukocytes can be infected with *S. neurona*,[49] and clinical signs have been observed in immunocompetent horses following the intravenous injection of *S. neurona*-infected autologous lymphocytes.[48] Alternatively, or perhaps also, the organism may enter the CNS directly through the cytoplasm of infected endothelial cells.[41]

Resistance to *S. neurona* is presumed to be due to the combined effects of humoral and cellular immunity. Following infection, there is a relatively rapid production of antibodies. In horses challenged with live *S. neurona* organisms orally, all horses seroconverted within 32 days,[19] while in another study, horses challenged with a larger number of organism seroconverted by day 13 after infection (if stressed by transport) and by day 30 in unstressed horses.[43] In immunocompetent mice, a vigorous humoral response is also noted, with seroconversion and increased B-cell numbers and proportions, associated with the development of germinal centers in lymphoid tissue.[50]

It has been demonstrated that antibody to various apicomplexan parasites such as *S. neurona* is protective. Invasion of target cells by *Trypanosoma cruzi* can be blocked by specific antibodies,[51] and treatment of immunocompromised patients with *Cryptosporidium parvum* using hyperimmunized plasma can eliminate clinical signs.[52] This has been shown to be a direct result of the presence of antibodies to specific cell-surface proteins.[53] Research with *S. neurona* has demonstrated that antibodies to the SN14 and SN16 surface proteins block target cell penetration, while blocking the SN30 surface protein had no effect.[54]

While the effects of circulating antibody are likely to be very important, cell-mediated immunity is necessary for the elimination of intracellular forms of most organisms. In immunocompetent mice, there is a significant increase in both total CD8+ splenocytes, as well as an increase in the percentage of CD8+ peripheral blood lymphocytes following infection with *S. neurona*.[50] Comparable studies have not been done in the horse; however, it has been found that peripheral blood and cerebrospinal fluid (CSF) lymphocyte subsets did not differ between horses with EPM and those that were normal.[55] However, this study was marred by small numbers of animals, and differences may have been obscured. Another study found that peripheral blood CD4+ lymphocytes were slightly decreased in seropositive horses that were demonstrating clinical signs, when compared to asymptomatic, seropositive horses. In this group, there was no change in the CD8+ subset.[56]

Mouse studies have confirmed the importance of CD8+ T cells in protection against *S. neurona* encephalopathy in that species. Endothelitis and meningoencephalitis developed in CD8-knockout (KO) mice following challenge with *S. neurona*, highlighting the importance of this cell subset in protection against *S. neurona.*[57] The CD8+ T cells (aka cytotoxic T cells) are one important source of interferon-gamma (IFN-γ), which is widely recognized as being important in the elimination of *Toxoplasma gondii*, a similar protozoan parasite.[58]

IFN-γ has also been found to be critical for protection against *S. neurona*-induced neurologic disease in mice.[59] Infection of IFN-γ KO mice leads to fulminant neurologic disease. Following infection with *S. neurona*, SCID mice do not develop neurologic disease, yet maintain a persistent low-level parasitemia following infection with *S. neurona*.[46] SCID mice are unable to mount adaptive immune responses, yet have natural killer (NK) cells which have the ability to secrete IFN-γ. When SCID mice were treated with neutralizing anti-IFN-γ antibody, neurologic disease resulted.[46] These findings support the critical importance of IFN-γ in protection against *S. neurona*.

These data also suggest an important role of the NK cell, which has been found to be critically important in the protection of other species from

protozoan parasites.[60] However, when NK cells were depleted in mice, then the mice infected with *S. neurona*, neurologic disease did not result.[46] The reasons for this are unknown, but could result from a failure to eliminate all NK cells, with some residual IFN-γ production, or the production of IFN-γ by non-NK cells. IFN-γ secreted by sensitized T cells activates macrophages, enabling them to kill intracellular organisms by promoting phagosome–lysosome fusion. One important mechanism by which activated macrophages kill parasite-infected target cells is via the production of nitric oxide (NO).

NO– is a multifunction molecule that acts as a neurotransmitter, vasodilator, and immune mediator. It arises as three isoforms (inducible NOS, endothelial NOS, and neuronal NOS), and all three have been reported in mammalian CSF.[61] Increased quantities of NO– have been found in association with infections of various parasitic protozoa, including *Babesia bovis*,[62] *T. cruzi*,[63] *T. brucei*, and *Plasmodium falciparum*, underscoring the importance of this protective mechanism in parasitic infections.[64]

In horses with EPM induced using the transport stress model, as well as in naturally occurring EPM, a decreased concentration of NO– in the CSF was found negatively associated with severity of clinical signs.[44] A clear interpretation of these results is not immediately obvious; however, it was suggested that the decrease could be simply a result of infection, and NO– was not protective. This is supported by work in iNOS and eNOS KO mice, in which it was found that these mice were resistant to the development of nervous system illness when infected with *S. neurona*.[65] It is important to recognize, however, that the iNOS KO mice had IFN-γ present in low concentrations, suggesting that only very low concentrations of IFN-γ are necessary for protection, and further highlighting the central role of IFN-γ in protection against *S. neurona*.

Epidemiologic studies have suggested that stress has at least a permissive effect upon the development of EPM; however, there is also evidence that the presence of the organism may itself be immunosuppressive. Cell-mediated immune responses to mitogens have been shown to be reduced in horses with EPM;[56] however, it is unclear whether this was a cause or effect of infection. In other studies, lymphocytes from EPM-positive horses had suppressed blast transformation when co-incubated with snSAG-1 protein that was not observed in lymphocytes from EPM-negative horses, nor when either cell type was stimulated with Con A.[66] This represents an antigen-specific immunosuppression of cellular response. Furthermore, IFN-γ messenger RNA production was diminished in lymphocytes from EPM-positive horses.[66] These were *in vitro* studies, which may not directly represent the *in vivo* situation, but even local immunosuppression in the microenvironment of the parasite is perhaps significant in an infected animal. In addition to possible immunosuppressive effects of the parasite itself, the unique environment of the CNS may also have a role in the pathophysiology of the infection.

Infection of the CNS is somewhat unique in that the CNS is considered an "immune-privileged site." This refers to the observation that the immune response in this tissue, while fully competent, differs from that of other tissues. Specifically, the immune system of the CNS appears to function to clear any infecting organism while minimizing inflammation.[67] This is perceived to have some survival benefit for the horse, for it may be that the inflammatory response in the CNS is more damaging than the initial insult that provokes it.[67] Modifications within the CNS to mediate the inflammatory response include a lack of conventional lymphatics, the presence of a blood–brain barrier (BBB) which minimizes but does not totally prohibit cellular surveillance of the CNS, and the presence of immunosuppressive cytokines which downregulate the vigor of the immune response.[68,69] A primary cytokine involved in immune privileged tissues is transforming growth factor-beta (TGF-β). This cytokine has numerous immune functions, depending upon its concentration and other cytokines present. TGF-β has been found in the CSF of many mammalian species and is considered one of the primary immunosuppressive cytokines in this tissue.[70] Mice infected with *T. cruzi* develop greater parasite burdens and die sooner when treated with TGF-β than untreated controls.[71] Even more dramatically, the *T. cruzi*-resistant mouse strain (C57BL/6 × DBA/2 F1) had a 50% mortality when treated with TGF-β compared to 0% mortality in untreated mice.[71] In addition, TGF-β blocks the production of IFN-γ,[72] this being the mechanism probably responsible for decreased parasite clearance in the presence of TGF-β. In mice, IFN-γ production was decreased when cells were co-incubated with CSF; an effect

that was reversed when TGF-β was blocked with specific monoclonal antibodies, thus confirming its role.[69]

TGF-β has been documented to be present in the CSF of the horse, and its concentration was found to be less in the CSF of horses with EPM.[73] Contrary to findings in mice, treatment of equine lymphocytes with CSF enhanced IFN-γ production, an effect that was not significantly affected by the application of TGF-β monoclonal antibodies.[73] These findings suggest that CSF is immunomodulatory in equine CSF; however, there appear to be other immunomodulatory proteins present as well.

CLINICAL SIGNS

Once the organism has infected the nervous system, it leads to localized inflammation with clinical neurologic signs which are dependent upon the anatomic site of the infection in the CNS. In general, *S. neurona*-induced neurologic disease results in clinical signs of muscle atrophy and ataxia, with asymmetry. Symmetrical illness can be seen however, and this should not lead one to exclude a diagnosis of EPM. Spinal cord symptoms predominate, leading to early signs of ataxia, stumbling, or weakness. Atrophy of the gluteal muscles is the most commonly affected muscle (54%), but any muscle can be involved, including the tongue.[36] In one series of cases, the progression of illness was most commonly chronic (47%), but was considered to be acute in 42% and peracute in 11% of cases.[36] Cranial nerve signs have been reported in up to 12% of reported cases.[36] These signs include muscle wasting of the temporalis and masseter muscles, head tilt, or dysphagia. Cerebral signs can also be seen, although rarely, and these include blindness, seizure activity, and altered mentation (Figures 15.1, 15.2).



Figure 15.1. Unilateral masseter muscle atrophy in a horse with EPM.

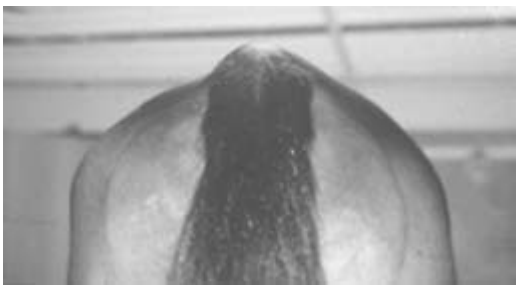


Figure 15.2. Left-sided gluteal muscle atrophy in a horse with EPM.

DIAGNOSIS

The clinical diagnosis of EPM remains a challenging task for veterinarians. Variable and sometimes subtle presentation of clinical signs and the inherent complexities of the diagnostic tests make a clear-cut and confirmed diagnosis of EPM in the clinical patient difficult. At present, the clinical diagnosis of EPM must be considered tentative in the live horse. Given these constraints, careful interpretation of clinical and ancillary diagnostic laboratory testing is the key to making a diagnosis. Diagnosis is dependent upon:

1. confirming the presence of clinical signs that are consistent with EPM
2. ruling out other potential causes of the observed clinical signs by appropriate means (spinal tap, radiography, serology, etc.)

3. confirming the presence of *S. neurona*-specific antibodies by one of a variety of means (i.e., immunodiagnostic testing)

Clinical Examination

Most people believe that a thorough physical and neurological examination remain the keystone of the EPM diagnosis.[74] For a diagnosis of EPM to be supported, conclusive evidence of CNS disease must be present. Musculoskeletal disease should be ruled out, if possible, by appropriate means. This may involve flexion tests and local nerve or joint blocks. Concurrent disease is possible and must be considered. The classic clinical signs of EPM have been well described and include gait abnormalities, and/or signs of cranial nerve, brainstem, or cerebral disease.[75] Asymmetry of clinical signs is a hallmark of the disease, although symmetrical deficits can be seen.

Once a physical examination is completed, ancillary testing is important to gather further information. The nature and extent of ancillary testing will be determined by the results of the neurologic exam; however, most commonly this will include radiographs of the cervical spine and a CSF collection and evaluation.

Eliminate Other Potential Causes

In the evaluation of a horse with potential EPM, it is important to consider a list of potential rule-outs in addition to EPM to help direct a full diagnostic evaluation. This will commonly include disorders such as cervical compressive myelopathy, trauma, or viral or bacterial neurologic disease, for example. Other causes include equine degenerative encephalomyelopathy, lower motor neuron disease, or developmental abnormalities. Survey radiographs, serology, and spinal fluid collection are all important components of a full evaluation. A full clinical examination to document the presence or absence of other clinical abnormalities, historical information, and routine clinicopathologic testing (complete blood count and serum chemistry profile) are usually warranted. A lameness examination is very important and should be carefully done to eliminate disease of the musculoskeletal system, as it is much more commonly affected than the CNS. If all such testing is negative, the probability of EPM increases, particularly if immunodiagnostic testing supports the diagnosis.

Cervical radiographs are indicated for the evaluation of any horses which have neuroanatomic localization of the clinical signs to the cervical region. While EPM does not cause radiographic changes, it is important to rule out other causes of spinal ataxia, such as cervical compression, fracture, or cervical facet arthritis, which may be present. If evidence of cervical compression is found, then myelography should be pursued.

CSF collection and evaluation is also recommended for full evaluation of the horse with CNS disease. CSF should be evaluated for red blood and nucleated cell count, total protein, and glucose concentrations, as well as a cytologic examination. A full evaluation of the CSF is important in identifying horses with viral or bacterial meningoencephalitis, tumors, or trauma. The CSF is usually normal in horses with EPM.

CSF concentration of the enzyme creatine kinase (CK) has been reported to have value in the differentiation of horses with EPM from those with cervical compressive myelopathy.[76] However, other research has questioned the validity of this approach, indicating that the CSF CK can become increased from traumatic puncture of the dura.[77] As in testing of any biochemical constituent of the CSF, the quality of the spinal fluid collection is important, and a traumatic tap or one in which multiple penetrations were necessary to obtain fluid, should lead to careful consideration of the validity of any constituent. This does not however, in itself, automatically invalidate the use of this CSF CK concentrations as a diagnostic aid. Hence, in the author's opinion, the use of CSF CK assay continues to have value on a properly collected (i.e., atraumatic) sample.

Immunodiagnostic Testing

The development of the immunoblot test (WB) for detection of *S. neurona*-specific antibodies was a great step forward in understanding EPM; however, its value as a diagnostic test has been questioned in recent years.[78,79] It was originally believed that the presence of *S. neurona*-specific antibodies in the CSF indicated the presence of active antibody production in the CNS, because in health no antibodies should pass the BBB. Clinical experience and definitive

empirical research have proven that this is not true. Many neurologically normal horses have been found to have antibodies to *S. neurona* in their CSF. In addition, antibodies to nonreplicating protein have been found in the CSF of vaccinated horses, directly correlating to plasma concentrations.[80] Hence, it is clear that in normal, healthy animals, there is some movement of antibody into the CSF. This finding clearly makes interpretation of CSF antibody tests more difficult than originally thought. The presence of antibodies in the CSF of healthy, noninfected animals is an issue that complicates the interpretation of any antibody-based test for EPM (Table 15.1).

Presence of antibodies in the serum only indicates exposure of the horse to the parasite, but not necessarily active disease. The presence of *S. neurona*-specific antibodies in CSF is more suggestive of infection, but is not definitive. Diagnostic testing using the serum and CSF WB test has been reported to have a sensitivity and specificity of approximately 89%, using histologically confirmed cases as the gold standard.[75] It was first presumed that *S. neurona* antibodies in CSF could only be present if the organism was present within the CNS. Several years of experience with this test have determined that this is not completely accurate. While

Table 15.1. Summary of Commercially Available Diagnostic Tests for EPM

Test Type and Source	Test Principle	Sensitivity/ Specificity (%)	Comments
Western blot (WB), EBI, Lexington	Detects the presence of antibodies to surface proteins	89/90[74]	Nonquantitative test
WB (modified), Michigan state	Detects the presence of antibodies to surface proteins after blocking with *Sarcocystis cruzi* antibodies	100/100[85]	Nonquantitative test
WB, Neogen, Inc.	Conventional WB	89/69[86]	Semiquantitative report (RQ) provided
Immunofluorescence (IFA), University of California, Davis	Detects the presence of antibodies to surface proteins	89/100	Quantitative method
SAG-1 ELISA Antech	Detects the presence of antibodies to a single *Sarcocystis neurona* surface protein	Not reported, similar test 68 / 71[90]	Quantitative

RQ, relative quotient.

S. neurona-specific antibodies are present in the CSF in active disease, false-positive results have been widely reported.[81,82] A number of mechanisms can give rise to this phenomenon.

In addition to blood contamination of the CSF sample during collection, it has been determined that circulating antibody (i.e., within plasma) can cross through an intact and healthy BBB leading to the presence of antibodies within the CSF.[80] This observation suggests that examination of paired serum and CSF WB results may be beneficial. If the serum reaction is strong, the corresponding CSF response should be robust to support a diagnosis of EPM.

The IgG_{index} is an ancillary diagnostic technique that is intended to determine whether the CSF IgG concentration exceeds that which is normally present from diffusion alone. In theory, a high IgG_{index} is supportive of IgG production within the CNS. Normal horses are reported to have an IgG_{index} of 0.30 or less.[83] Conflicting results have been reported regarding the utility and value of the IgG_{index} as a diagnostic aid in EPM. The IgG_{index} was found in one study to be higher than normal in horses with EPM;[84] however, subsequent research has not supported this initial observation.[85] It appears that the IgG_{index} provides only limited diagnostic information, and its routine use as a diagnostic for EPM is not recommended.[74] Additional antigen-specific measures of determining intrathecal antibody production have been proposed, but have not been specifically evaluated for their diagnostic performance in horses with EPM.[80] These are discussed in more detail in Section 1, Chapter 3.

The standard or conventional WB (cWB) test has been modified at one testing laboratory (Michigan State) by blocking the 30-kD band with pooled serum with a high anti-*S. cruzi* antibody titer.[86] This is considered by them to be a cross-reacting antigen. This modified WB (mWB) was reported to have a sensitivity and specificity approaching 100%.[86] However, this study was performed on only a small number of EPM-positive horses (6), and subsequent evaluation of the mWB by other investigators has found a much lower sensitivity and specificity of 89 and 69%, respectively.[87] A further modification of the WB has been proposed by another testing laboratory (Neogen, Inc.), in which the intensity of the staining reaction of the 17-kD band is reported as a unitless number referred to as the "relative quotient" (RQ). This number ranges from 0 to 100, with a higher value implying a more robust antibody response against the 17-kD *S. neurona* surface protein. The use of the RQ has not been found to improve diagnostic efficiency, although in one study, the RQ did decrease slightly during treatment.[85]

A whole-organism indirect fluorescent antibody test (IFAT) has been developed and is currently available from the University of California Diagnostic Laboratory.[88] Diagnostic performance of the IFAT was tested and compared to the cWB and mWB and was reported to have a (slightly) better diagnostic efficiency than either test.[87] Serum titers of greater than 1:100 and CSF titers of greater than 1:5 were considered positive and diagnostic of active infection. Previous attempts using an IFA were disappointing, however, and the IFA was unable to distinguish between related *Sarcocystis* organisms.[89] This finding was further supported using the California IFAT, when it was demonstrated that the test was unable to differentiate between *S. neurona* and *S. fayeri* (a nonpathogenic *Sarcocystis*) infections.[90] Therefore, the superiority of the IFAT as a diagnostic for EPM is not clearly established and awaits further evaluation.

Another diagnostic test described for EPM is an enzyme-linked immunosorbent assay (ELISA) for antibodies to the snSag-1 protein. This test is currently commercially available from Antech, Inc. This test provides a titer, and values greater than 1:100 in serum are reported to indicate active infection.[48] Use of this test is not without concern, however. The test has not been rigorously evaluated for sensitivity and specificity, and the cut-off values for a positive diagnosis appear to be arbitrary. Further, it has been clearly demonstrated that not all *S. neurona* isolated produce the SAG-1 protein, hence false-negative results are possible with this test.

Another series of ELISA tests have been developed in another research laboratory to detect the presence of specific antibodies to various *S. neurona* surface antigens (*sn*SAG-1–4).[91] Using this test, a sensitivity and specificity of 95.5 and 92.9% was found for the snSAG-2 antigen, while sensitivity and specificity using the snSAG-1 antigen was only 68.2 and 71.4%, respectively. This suggests that the snSAG-1 surface protein may not be a reliable marker for detecting antibody specific for *S. neurona*.[91] This is consistent with previous work,

which has demonstrated that the 30-kD antigen (i.e., snSAG-1) was inconsistently reported.[5,8]

A stall-side *S. neurona* screening test is currently available for the confirmation of antibodies to *S. neurona* (*S. neurona*, Endocrine Technologies) in serum. This test uses the ELISA platform and snSag-1 as the antigen, as well as a second testing "spot" for mixed surface proteins. Presence of antibodies to both spots is considered diagnostic for EPM caused by *S. neurona*, while a positive reaction at either spot alone is considered suggestive, and the sample should be further tested and a specific titer determined. The sensitivity and specificity of this test kit has not been determined. It may have value as a screening test but probably should not be used alone for diagnostic confirmation.

In conclusion, it seems that the ideal diagnostic test does not yet exist for the clinical diagnosis of EPM. Diagnosis in a clinical patient is best supported by the finding of definitive CNS abnormalities on a neurologic exam, the elimination of other neurologic diseases by radiography and CSF evaluation, and the finding of *S. neurona*-specific antibodies in appropriately collected CSF by WB or IFAT.

TREATMENT

The use of antiprotozoal compounds is the cornerstone of treatment for EPM. Recognition of the role of protozoa in EPM led to the use of trimethoprim and sulfonamide compounds to treat horses.[92] The clinical results from many investigators were favorable, and this class of drug was widely used in the treatment of EPM for many years. A variety of new compounds have been developed subsequently and are licensed for treatment of EPM in the United States. In addition to ponazuril, which was the first FDA-approved EPM medication, nitazoxanide (NTZ) (Navigator) and a sulfadiazine/pyrimethamine combination drug (Re-Balance) are currently approved for treatment of EPM (Table 15.2).

A widely used and recommended drug for the treatment of EPM is ponazuril (Marquis, Bayer Animal Health), dosed at 5 mg/kg per day for a minimum of 28 days. Ponazuril appears to act by inhibition of the respiratory chain enzymes of the *S. neurona* apicoplast and mitochondria.[93,94] Ponazuril is a triazinetrione class drug which is technically considered to be protozoastatic in its action, based on *in vitro* techniques.[95] The significance of this finding *in vivo*, however, is totally unknown and is probably unimportant as efficacy studies between protozoacidal and protozoastatic drugs provide similar outcomes.

Ponazuril is well absorbed orally and achieves a steady-state concentration of 0.16 ± 0.06 mg/l in the CSF of horses treated with 5 mg/kg body weight.[96] *In vitro* studies have documented that concentrations of 0.1 μg/ml resulted in a 94.4% reduction in *S. neurona* production.[97]

A field efficacy study of 101 horses has demonstrated approximately 60% efficacy, with 8% relapse within 90 days following the termination of treatment.[85] Animals typically responded within 10 days and often continued to improve even after treatment stopped at 28 days. The baseline neurologic score

Table 15.2. Comparative Summary of Clinical Efficacy Testing for Various Antiprotozoal Drugs

Drug	N1	N2	Duration (days)	Dose (mg/kg)	Days Follow-up	Success (%)
NTZ	96	49	28	25/50	57	57
NTZ	419	250	28	25/50	57	81*
Ponaz	53	47	5	28	90	60
Ponaz	60	55	10	28	90	58
S/P	48	26	90–270	20/1	Various	61
DCZ	72	49	28	1	20	58

N1, number enrolled; N2, number completed; NTZ, nitazoxanide; Ponaz, ponazuril; S/P, sulfadiazine pyrimethamine combination; DCZ, diclazuril.

*Results of a study protocol which differed significantly from the others reported.

did not influence outcome in that study; however, success was defined as improvement by one clinical grade, which may be considered unacceptable in severe cases.[85] In clinical cases, the author routinely re-evaluates the animal at the end of the treatment period, then makes a determination if further treatment is needed. In general, if there has been a clinical response, yet the horse remains abnormal, a second month of ponazuril is recommended. Extended dosing may reduce the occurrence of relapse, but this has not been empirically evaluated. If finances are limited, then treatment can stop after 28 days, but the horse should be reexamined in one month to ensure that there is no deterioration.

Safety studies have found ponazuril to be very safe, with no systemic toxicity, even at high doses (30 mg/kg body weight) for up to 56 days.[98] Uterine edema was noted in mares given 30 mg/day weight for 30 days, however.[98] Treatment of breeding stallions with 10 mg/kg body weight ponazuril did not affect androgenic hormone production nor spermatogensis.[99] Ponazuril has been used without obvious problems in pregnant mares, but the use of ponazuril in pregnant animals is off-label, and owners should be made aware of this fact. Feeding 2 ounces of corn oil immediately before the ponazuril is given results in blood concentrations which are 25% higher than if no corn oil is given.[100] The author routinely recommends this approach.

NTZ (Navigator, Idexx Pharmaceuticals) has also been approved by the FDA for the treatment of EPM. NTZ is a member of the 5-nitrothiazol class of antimicrobials. NTZ also demonstrated a success rate of about 60% in horses in a well-controlled clinical field trial, which was scrutinized by the FDA, and which was comparable in design to the ponazuril study.[101] A second, much less well-controlled study of this drug reported a higher success rate and is the basis for much advertising.[101] In the second study, a success rate of 81% was reported. However, the standards for diagnosis and case inclusion were very different than the other studies, and it is very inappropriate to make comparisons between this study and the FDA-controlled studies for the other compounds.

NTZ has a wide range of effects, including antibacterial, antiprotozoal, and antiparasitic activity.[102] Minimal pharmacokinetic data are available for the horse; however, following dosing with 50 mg/kg body weight, peak steady-state serum concentrations of 0.97 μg/ml were found.[101] *In vitro* testing suggests that the effective concentration for the active metabolite of NTZ (tizoxanide) is greater the 5.0 μg/ml. CNS or CSF concentrations of either NTZ or tizoxanide have not been published.

There are concerns regarding the toxicity of NTZ. In safety testing, horses became very ill at 2× the dose, and there were some deaths at 3× after only a few doses.[95] Modification of the dosing schedule has reduced the apparent side effects, and in field use much less toxicity was observed; however, some diarrhea, depression, and laminitis were seen. Results of the field efficacy studies for NTZ also demonstrate that only 51–59% of enrolled horses completed the study, suggesting toxicity issues. This is in contrast to a completion rate of 68% for diclazuril and 90% (combined) for the ponazuril study. To minimize toxicity, horses are given half the dose each day, then the dose is increased for the final 21 days of treatment. Although the field use of this drug has not been associated with as much toxicity as some feared, it must be carefully dosed to minimize toxicity, and this author has seen toxicity even after carefully following the treatment schedule.

Historically, a combination of sulfonamide and pyrimethamine (S/P) has been used to treat EPM. This was based on the effectiveness of this class of compounds upon malaria and other protozoan infections.[92] This combination has been compounded, but recently a premixed version of this combination has achieved FDA approval and can be purchased (ReBalance, Phoenix Scientific). The sulfonamide component of this compound competes with paraaminobenzoic acid (PABA) to decrease folate metabolism, while the pyrimethamine competes with dihydrofolate reductase (DHFR), minimizing folate synthesis. The synergistic effects of these compounds lead to destruction of the *S. neurona* organism. A field efficacy study reported a success rate of 57% after several months of treatment.[95] Weaknesses of S/P suspension in the treatment of EPM include the prolonged duration of treatment required to affect a positive response and the toxicity of the compound. Toxicity includes anemia, fetal loss, and fetal abnormalities. A benefit of S/P combinations is the lower cost, yet this may be offset by the extended dosing interval required.

Pyrimethamine has historically been given in combination with sulfa drugs in the treatment of EPM. There is, however, some evidence to suggest a synergistic effect of pyrimethamine when used with the triazine-group antiprotozoals. While not empirically evaluated in horses with EPM, it may be beneficial to add this drug to the treatment regimen. This can be added to the treatment in refractory cases, but its effectiveness is not known at this time.

In addition to the drugs mentioned above, diclazuril has been critically evaluated and is currently under review by the FDA for approval for the treatment of EPM caused by *S. neurona*. An approval and release date for this product has not been announced at the time of this writing; however, the proposed trade name of the drug is Protazil and a success rate of 58% was reported.[95]

The duration of treatment for EPM is difficult to determine, and when to terminate treatment in any one particular horse remains problematic. Duration of treatment appears to be more important than peak concentrations (as long as they exceed MIC). Hence, the author's approach is to evaluate horses after 1 month of treatment with ponazuril or diclazuril. If improvement has been noted, but clinical signs remain, then a further month of treatment is recommended. If finances are limiting, or the horse appears clinically normal, then treatment can be discontinued, but the horse should be examined 1 month after treatment is completed to ensure that there has been no relapse. Alternatively, a 1- to 2-month course of S/P can be given to help minimize the chance of recrudescence.

Treatment until the CSF WB becomes negative has been advocated by some clinicians in the past.[103] This seems an unachievable goal for most cases, as horses will carry a positive titer for long periods; this recommendation is rarely followed.

Ancillary treatments may include various anti-inflammatory drugs such as phenylbutazone, flunixen meglumine, dimethyl sulfoxide (DMSO) (IV or oral), or steroids. Corticosteroids can be used to help stabilize horses with serious neurologic abnormalities during the early period of treatment. Long-term steroids should be avoided due to their unknown effects upon immune clearance of the organism. Some clinicians have reported that horses initially worsen with treatment, and recommend prophylactic use of nonsteroidal antiinflammatory drugs (NSAIDs) to ameliorate this "treatment crisis." In the author's experience, this is rarely a problem, hence the author does not recommend using NSAIDs routinely unless worsening of signs is seen. Additional ancillary treatments, such as vitamin E, homeopathic medications, and so on, have not been demonstrated to have any value, and the author does not recommend these compounds or approaches. In addition, immunostimulants have been recommended by some authors, on the presumption that immunosuppression is a component of the pathophysiology of EPM. Levamisole (1 mg/kg PO daily), Eqstim (5 ml IM on days 1, 3, and 7, then monthly), or Equimune IV (1.5 ml IV weekly for 3 weeks) have all been advocated; however, there is no specific information to suggest that these have any positive effect.

PROGNOSIS

Based on clinical experience and reported efficacy studies, it appears that 60% of affected horses will improve by at least one neurologic grade after treatment. Up to 20% may recover completely, that is, return to neurologic normalcy. Prompt treatment of suspect and less severe cases is more likely to have the best outcome, and a success rate of up to 80% has been suggested for such cases.[95]

PREVENTION

The prevention of EPM remains a poorly investigated area. Simple measures such as removing spilled grain, fallen fruit, and animal or bird feed which might attract intermediate hosts to the horse environment are probably useful. Grain stores should be secured such that foraging intermediate hosts cannot gain access and contaminate feed. Removal of intermediate hosts in an effort to reduce pasture contamination is probably futile.

A vaccine has been developed and marketed by Fort Dodge Animal Health and is currently for sale in most states of the US. At the present time, however, the vaccine is approved on only a conditional basis, which can be withdrawn at any time. As of this writing, challenge studies have been completed but not reported. Field safety studies with almost 900 horses demonstrated that the compound is safe.[95] Vaccinated horses may become WB positive

in the CSF, but usually transiently.[104] Hence, knowledge of vaccination status is important in the proper interpretation of CSF immunoassays. Recommendations about the use of this vaccine depend upon the local risk of infection, clear understanding that efficacy is not proven, and the knowledge that immunodiagnostic testing if necessary will be more challenging to interpret. Given the apparent safety, and the considerations about immune protection noted above, its use in endemic areas is reasonable.

The use of pharmaceutical agents to prevent EPM has been demonstrated by continuous pretreatment with ponazuril in horses.[105] At 5 mg/kg body weight once daily, the incidence of clinical EPM was dramatically reduced following challenge with infective sporocysts.[105] This treatment did not completely eliminate clinical disease, however. While effective, it is not likely to be cost effective to maintain a horse on the drug continuously, but may be useful in particular situations in which the risk of contracting EPM is increased, such as associated with stressful events, showing, or shipping. Intermittent (weekly) dosing with ponazuril at 20 mg/kg body weight reduced CSF antibody development in challenged horses and may be a more cost-effective option than continuous treatment.[95] Other pharmaceutical approaches, such as the use of pyrantel pamoate, have not proven effective and are not advised.

REFERENCES

1. Rooney JR, Prickett ME, Delaney FM, *et al*. 1969. Focal myelitis-encephalitis in horses. *Cornell Vet* 60:494–501.
2. Beech J, Dodd DC. 1974. Toxoplasma-like encephalomyelitis in the horse. *Vet Pathol* 11: 87–96.
3. Dubey JP. 1976. A review of *Sarcocystis* of domestic animals and of other coccidia of cats and dogs. *J Am Vet Med Assoc* 169:1061–78.
4. Dubey JP, Davis SW, Speer CA, *et al*. 1991. *Sarcocystis neurona* n. sp. (Protozoa: Apicomplexa), the etiologic agent of equine protozoal myeloencephalitis. *J Parasitol* 77:212–8.
5. Marsh AE, Johnson PJ, Ramos Vara J, *et al*. 2001. Characterization of a *Sarcocystis neurona* isolate from a Missouri horse with equine protozoal myeloencephalitis. *Vet Parasitol* 95:143–54.
6. Dubey JP, Mattson DE, Speer CA, *et al*. 1999. Characterization of a *Sarcocystis neurona* isolate (SN6) from a naturally infected horse from Oregon. *J Eukaryot Microbiol* 46:500–6.
7. Dubey JP, Mattson DE, Speer CA, *et al*. 2001. Characteristics of a recent isolate of *Sarcocystis neurona* (SN7) from a horse and loss of pathogenicity of isolates SN6 and SN7 by passages in cell culture. *Vet Parasitol* 95:155–66.
8. Hyun C, Gupta GD, Marsh AE. 2003. Sequence comparison of *Sarcocystis neurona* surface antigen from multiple isolates. *Vet Parasitol* 112:11–20.
9. Mansfield LS, Schott HC, II, Murphy AJ, *et al.* 2001. Comparison of *Sarcocystis neurona* isolates derived from horse neural tissue. *Vet Parasitol* 95:167–78.
10. Marsh AE, Denver M, Hill FI, *et al.* 2000. Detection of *Sarcocystis neurona* in the brain of a Grant's zebra (*Equus burchelli bohmi*). *J Zoo Wildl Med* 31:82–6.
11. Dubey JP, Benson J, Larson MA. 2003. Clinical *Sarcocystis neurona* encephalomyelitis in a domestic cat following routine surgery. *Vet Parasitol* 112:261–7.
12. Forest TW, Abou-Madi N, Summers BA, *et al*. 2000. *Sarcocystis neurona*-like encephalitis in a Canada lynx (*Felis lynx canadensis*). *J Zoo Wildl Med* 31:383–7.
13. Lindsay DS, Thomas NJ, Dubey JP. 2000. Biological characterisation of *Sarcocystis neurona* isolated from a Southern sea otter (*Enhydra lutris nereis*). *Int J Parasitol* 30:617–24.
14. Dubey JR, Rosypal AC, Rosenthal BM, *et al*. 2001. *Sarcocystis neurona* infections in sea otter (*Enhydra lutris*): evidence for natural infections with sarcocysts and transmission of infection to opossums (*Didelphis virginiana*). *J Parasitol* 87:1387–93.
15. Dubey JR, Johnson GC, Bermudez A, *et al*. 2001. Neural sarcocystosis in a straw-necked ibis (*Carphibis spinicollis*) associated with a *Sarcocystis neurona*-like organism and description of muscular sarcocysts of an unidentified Sarcocystis species. *J Parasitol* 87:1317–22.
16. Dubey JP, Hamir AN, Niezgoda M, *et al*. 1996. A *Sarcocystis neurona*-like organism associated with encephalitis in a striped skunk (*Mephitis mephitis*). *J Parasitol* 82:172–4.
17. Dubey JP, Hedstrom OR. 1993. Meningoencephalitis in mink associated with a *Sarcocystis neurona*-like organism. *J Vet Diagn Invest* 5:467–71.
18. Dubey JP, Hamir AN. 2000. Immunohistochemical confirmation of *Sarcocystis neurona* infections in raccoons, mink, cat, skunk, and pony. *J Parasitol* 86:1150–2.
19. Cutler TJ, MacKay RJ, Ginn PE, *et al*. 2001. Immunoconversion against *Sarcocystis neurona*

in normal and dexamethasone-treated horses challenged with *S. neurona* sporocysts. *Vet Parasitol* 95:197–210.
20. Sofaly CD, Reed SM, Gordon JC, *et al*. 2002. Experimental induction of equine protozoan myeloencephalitis (EPM) in the horse: effect of *Sarcocystis neurona* sporocyst inoculation dose on the development of clinical neurologic disease. *J Parasitol* 88:1164–70.
21. Fenger CK, Granstrom DE, Gajadhar AA, *et al*. 1997. Experimental induction of equine protozoal myeloencephalitis in horses using *Sarcocystis* sp. sporocysts from the opossum (*Didelphis virginiana*). *Vet Parasitol* 68:199–213.
22. Ellison SB, Greiner E, Brown KK, *et al*. 2004. Experimental infection of horses with culture-derived *Sarcocystis neurona* merozoites as a model for equine protozoal myeloencephalitis. *Int J Appl Res Vet Med* 2:79–89.
23. Marsh AE, Barr BC, Madigan J, *et al*. 1996. Neosporosis as a cause of equine protozoal myeloencephalitis. *J Am Vet Med Assoc* 209:1907–13.
24. Hamir AN, Tornquist SJ, Gerros TC, *et al*. 1998. *Neospora caninum*-associated equine protozoal myeloencephalitis. *Vet Parasitol* 79:269–74.
25. Cusick PK, Sells DM, Hamilton DP, *et al*. 1974. Toxoplasmosis in two horses. *J Am Vet Med Assoc* 164:77–80.
26. Simpson CF, Mayhew IG. 1980. Evidence for Sarcocystis as the etiologic agent of equine protozoal myeloencephalitis. *J Protozoal* 27: 288–92.
27. Pitel PH, Pronost S, Gargala G, *et al*. 2002. Detection of *Sarcocystis neurona* antibodies in French horses with neurological signs. *Int J Parasitol* 32:481–5.
28. Goehring LS, Sloet van Oldruitenborgh-Oosterbaan MM. 2001. [Equine protozoal myeloencephalitis in the Netherlands? An overview.]. *Tijdschr Diergeneeskd* 126:346–51.
29. Rossano MG, Kaneene JB, Marteniuk JV, *et al*. 2001. The seroprevalence of antibodies to *Sarcocystis neurona* in Michigan equids. *Prev Vet Med* 48:113–28.
30. Blythe LL, Granstrom DE, Hansen DE, *et al*. 1997. Seroprevalence of antibodies to *Sarcocystis neurona* in horses residing in Oregon. *J Am Vet Med Assoc* 210:525–7.
31. Bentz BG, Ealey KA, Morrow J, *et al*. 2003. Seroprevalence of antibodies to *Sarcocystis neurona* in equids residing in Oklahoma. *J Vet Diagn Invest* 15:597–600.
32. Saville WJ, Reed SM, Granstrom DE, *et al*. 1997. Seroprevalence of antibodies to *Sarcocystis neurona* in horses residing in Ohio. *J Am Vet Med Assoc* 210:519–24.
33. Fenger CK. 1997. Equine protozoal myeloencephalitis. *Compend Contin Educ Pract Vet* 19:513–23, 34.
34. Vardeleon D, Marsh AE, Thorne JG, *et al*. 2001. Prevalence of *Neospora hughesi* and *Sarcocystis neurona* antibodies in horses from various geographical locations. *Vet Parasitol* 95:273–82.
35. Duarte PC, Conrad PA, Wilson WD, *et al*. 2004. Risk of postnatal exposure to *Sarcocystis neurona* and *Neospora hughesi* in horses. *Am J Vet Res* 65:1047–52.
36. Mayhew IG, De Lahunta A, Whitlock RH, *et al*. 1977. Equine protozoal myeloencephalitis. *Proc Annu Meet Am Assoc Equine Pract* 22:107–14.
37. Boy MG, Galligan DT, Divers TJ. 1990. Protozoal encephalomyelitis in horses: 82 cases (1972–1986). *J Am Vet Med Assoc* 196:632–4.
38. Gray LC, Magdesian KG, Sturges BK, *et al*. 2001. Suspected protozoal myeloencephalitis in a two-month-old colt. *Vet Rec* 149:269–73.
39. MacKay RJ, Davis SW, Dubey JP. 1992. Equine protozoal myeloencephalitis. *Compend Contin Educ Pract Vet* 14:1359–67.
40. Fayer R, Mayhew IG, Baird JD, *et al*. 1990. Epidemiology of equine protozoal myeloencephalitis in North America based on histologically confirmed cases. *J Vet Intern Med* 4:54–7.
41. Dubey JP. 2001. Migration and development of *Sarcocystis neurona* in tissues of interferon gamma knockout mice fed sporocysts from a naturally infected opossum. *Vet Parasitol* 95: 341–51.
42. Saville WJ, Morley PS, Reed SM, *et al*. 2000. Evaluation of risk factors associated with clinical improvement and survival of horses with equine protozoal myeloencephalitis. *J Am Vet Med Assoc* 217:1181–5.
43. Saville WJ, Stich RW, Reed SM, *et al*. 2001. Utilization of stress in the development of an equine model for equine protozoal myeloencephalitis. *Vet Parasitol* 95:211–22.
44. Njoku CJ, Saville WJ, Reed SM, *et al*. 2002. Reduced levels of nitric oxide metabolites in cerebrospinal fluid are associated with equine protozoal myeloencephalitis. *Clin Diagn Lab Immunol* 9:605–10.
45. Mullaney T, Murphy AJ, Kiupel M, *et al*. 2005. Evidence to support horses as natural intermediate hosts for *Sarcocystis neurona*. *Vet Parasitol* 133:27–36.
46. Sellon DC, Knowles DP, Greiner EC, *et al*. 2004. Depletion of natural killer cells does not result in

neurologic disease due to *Sarcocystis neurona* in mice with severe combined immunodeficiency. *J Parasitol* 90:782–8.
47. Rossano MG, Schott HC, Murphy AJ, *et al*. 2005. Parasitemia in an immunocompetent horse experimentally challenged with *Sarcocystis neurona* sporocysts. *Vet Parasitol* 127:3–8.
48. Ellison SP, Kennedy T, Brown KK. 2003. Development of an ELISA to detect antibodies to rSAG1 in the horse. *J Appl Res Vet Med* 1:318–27.
49. Lindsay DS, Mitchell SM, Yang J, *et al*. 2006. Penetration of equine leukocytes by merozoites of *Sarcocystis neurona*. *Vet Parasitol* 138:371–6.
50. Witonsky SG, Gogal RM, Jr., Duncan RB, *et al*. 2003. Protective immune response to experimental infection with *Sarcocystis neurona* in 57BL/6 mice. *J Parasitol* 89:924–31.
51. Alvers MJ, Abuin G, Kuwajima VY, *et al*. 1986. Partial inhibition of trypomastigote entry into cultured mammalian cells by monoclonal antibodies against a surface glycoprotein of *Trypanosoma cruzi*. *Mol Biochem Parasitol* 21:75–82.
52. Tzipori S, Robertson D, Cooper D, *et al*. 1987. Chronic cryptosporidiosis and hyperimmune bovine colostrum. *Lancet* ii:344–5.
53. Doyle PS, Crabb J, Peterson C. 1993. Anti-*Cryptosporidium parvum* antibodies inhibit infectivity in vitro and in vivo. *Infect Immun* 61: 4079–84.
54. Liang FT, Granstrom DE, Zhao XM, *et al*. 1998. Evidence that surface proteins Sn14 and Sn16 of *Sarcocystis neurona* merozoites are involved in infection and immunity. *Infect Immun* 66:1834–8.
55. Furr M, Pontzer C, Gasper P. 2001. Lymphocyte phenotype subsets in the cerebrospinal fluid of normal horses and horses with equine protozoal myeloencephalitis. *Vet Ther* 2:317–24.
56. Tornquist SJ, Boeder LJ, Mattson DE, *et al*. 2001. Lymphocyte responses and immunophenotypes in horses with *Sarcocystis neurona* infection. *Equine Vet J* 33:726–9.
57. Witonsky SG, Gogal RM, Jr., Duncan RB, Jr., *et al*. 2005. Prevention of meningo/encephalomyelitis due to *Sarcocystis neurona* infection in mice is mediated by CD8 cells. *Int J Parasitol* 35:113–23.
58. Suzuki Y, Orrelman M, Schreiber R, *et al*. 1988. Interferon-γ; the major mediator of resistance against *Toxoplasma gondii*. *Science* 240:516–8.
59. Dubey JP, Lindsay DS. 1998. Isolation in immunodeficient mice of *Sarcocystis neurona* from opossum (*Didelphis virginiana*) faeces, and its differentiation from *Sarcocystis falcatula*. *Int J Parasitol* 28:1823–8.
60. Denkers EY, Gazzinelli RT, Martin D, *et al*. 1993. Emergence of NK1.1+ cells as effectors of IFN-gamma dependent immunity to *Toxoplasma gondii* in MHC class I-deficient mice. *J Exp Med* 178:1465–72.
61. Dawson VL, Dawson TM. 1996. Nitric oxide actions in neurochemistry. *Neurchem Int* 29:97–110.
62. Stich RW, Shoda L, Dreewes M, *et al*. 1998. Stimulation of nitric oxide production in macrophages by *Babesia bovis*. *Infect Immun* 66: 4130–6.
63. Metz G, Carlier Y, Vray B. 1993. *Trypanosoma cruzi* upregulates nitric oxide release by IFN-gamma-preactivated macrophages, limiting cell infection independently of the respiratory burst. *Parasite Immunol* 15:693–9.
64. Shoda L, Kegerreis K, Suarez E, *et al*. 2001. DNA from protozoan parasites *Babesia bovis, Trypanosoma cruzi*, and *T. brucei* is mitogenic for B lymphocytes and stimulates macrophage expression of interleukin-12, tumor necrosis factor alpha, and nitric oxide. *Infect Immun* 69:2162–71.
65. Rosypal AC, Lindsay DS, Duncan R, Jr., *et al*. 2002. Mice lacking the gene for inducible or endothelial nitric oxide are resistant to sporocyst induced *Sarcocystis neurona* infections. *Vet Parasitol* 103:315–21.
66. Spencer JA, Ellison SE, Guarino AJ, *et al*. 2004. Cell-mediated immune responses in horses with equine protozoal myeloencephalitis. *J Parasitol* 90:428–30.
67. Cserr HF, Knopf PM. 1992. Cervical lymphatics, the blood–brain barrier and the immunoreactivity of the brain: a new view. *Immunol Today* 13: 507–12.
68. Taylor A, Streilein J. 1996. Inhibition of antigen stimulated effector T cells by human cerebrospinal fluid. *Neuroimmunomodulation* 3: 112–8.
69. Taylor AW. 1996. Neuroimmunomodulation in immune privilege: role of neuropeptides in ocular immunosuppression. *Neuroimmunomodulation* 3:195–204.
70. Wilbanks G, Streilein J. 1992. Fluids from immune privileged sites endow macrophages with the capacity to induce antigen-specific immune deviation via a mechanism involving transforming growth factor-β. *Eur J Immunol* 22:1031–6.
71. Silva JC, Twardzik D, Reed S. 1991. Regulation of *Trypanosoma cruzi* infection *in vitro* and *in*

vivo by transforming growth factor β (TGF-β). *J Exp Med* 174:539–45.
72. Letterio J, Roberts A. 1997. TGF-β; a critical modulator of immune cell function. *Clin Immunol Immunopathol* 84:244–50.
73. Furr M, Pontzer C. 2001. Transforming growth factor beta concentrations and interferon gamma responses in cerebrospinal fluid of horses with equine protozoal myeloencephalitis. *Equine Vet J* 33:721–5.
74. Furr M, MacKay R, Granstrom D, *et al*. 2002. Clinical diagnosis of equine protozoal myeloencephalitis (EPM). *J Vet Intern Med* 16:618–21.
75. Dubey JP, Lindsay DS, Saville WJA, *et al*. 2001. A review of *Sarcocystis neurona* and equine protozoal myeloencephalitis (EPM). *Vet Parasitol* 95:89–131.
76. Furr MO, Tyler RD. 1990. Cerebrospinal fluid creatine kinase activity in horses with central nervous system disease: 69 cases (1984–1989). *J Am Vet Med Assoc* 197:245–8.
77. Jackson C, DeLahunta A, Divers TJ, *et al*. 1996. The diagnostic utility of cerebrospinal fluid creatine kinase activity in the horse. *J Vet Intern Med* 10:246–51.
78. Granstrom D. 1993. Diagnosis of equine protozoal myeloencephalitis: western blot analysis. *Proc 21st Annual Meet ACVIM*, 587–90.
79. Miller MM, Sweeney CR, Russell GE, *et al*. 1999. Effects of blood contamination of cerebrospinal fluid on western blot analysis for detection of antibodies against *Sarcocystis neurona* and on albumin quotient and immunoglobulin G index in horses. *J Am Vet Med Assoc* 215:67–71.
80. Furr M. 2002. Antigen-specific antibodies in cerebrospinal fluid after intramuscular injection of ovalbumin in horses. *J Vet Intern Med* 16:588–92.
81. Bentz BG, Carter WG, Tobin T. 1999. Diagnosing equine protozoal myeloencephalitis: complicating factors. *Compend Contin Educ Pract Vet* 21:975–81, 86–87.
82. Cook AG, Maxwell VB, Donaldson LL, *et al*. 2002. Detection of antibodies against *Sarcocystis neurona* in cerebrospinal fluid from clinically normal neonatal foals. *J Am Vet Med Assoc* 220:208–11.
83. Andrews F, Maddux J, Faulk B. 1990. Total protein, albumin quotient, IgG and IgG index determinations for horse cerebrospinal fluid. *Prog Vet Neurol* 1:197–204.
84. Andrews FM, Latimer F, Grubbs S, *et al*. 1997. CSF indices after repeated spinal taps in horses diagnosed with equine protozoal myeloencephalitis. *Proc Annu Conv Am Assoc Equine Pract* 43:10–12.
85. Furr M, Kennedy T, MacKay R, *et al.* 2001. Efficacy of ponazuril 15% oral paste as a treatment for equine protozoal myeloencephalitis. *Vet Ther* 2: 215–22.
86. Rossano MG, Mansfield LS, Kaneene JB, *et al*. 2000. Improvement of western blot test specificity for detecting equine serum antibodies to *Sarcocystis neurona*. *J Vet Diagn Invest* 12: 28–32.
87. Duarte PC, Daft BM, Conrad PA, *et al*. 2003. Comparison of a serum indirect fluorescent antibody test with two Western blot tests for the diagnosis of equine protozoal myeloencephalitis. *J Vet Diagn Invest* 15:8–13.
88. Duarte PC, Daft BM, Conrad PA, *et al*. 2004. Evaluation and comparison of an indirect fluorescent antibody test for detection of antibodies to *Sarcocystis neurona*, using serum and cerebrospinal fluid of naturally and experimentally infected, and vaccinated horses. *J Parasitol* 90:379–86.
89. Granstrom DE. 1995. Equine protozoal myeloencephalitis testing: review of 1993 and 1994. *Proc Annu Conv Am Assoc Equine Pract* 41:218–9.
90. Saville WJ, Dubey JP, Oglesbee MJ, *et al*. 2004. Experimental infection of ponies with *Sarcocystis fayeri* and differentiation from *Sarcocystis neurona* infections in horses. *J Parasitol* 90: 1487–91.
91. Hoane JS, Morrow J, Saville WJ, *et al*. 2005. Enzyme-linked immunosorbent assays for detection of equine antibodies specific to *Sarcocystis neurona* surface antigens. *Clin Diagn Lab Immunol* 12:1050–6.
92. Beech J. 1974. Equine protozoal myeloencephalitis. *Vet Med Small Anim Clin* 69: 1562–6.
93. Harder A, Haberkorn A. 1989. Possible mode of action of toltrazuril: studies on two Eimeria species and mammalian and *Ascarus suum* enzymes. *Parasitol Res* 76:8–12.
94. Mitchell SM, Zajac AM, Davis WL, *et al*. 2005. The effects of ponazuril on development of apicomplexans *in vitro*. *J Eukaryot Microbiol* 52:231–5.
95. MacKay RJ. 2006. Equine protozoal myeloencephalitis: treatment, prognosis and prevention. *Clin Tech Equine Pract* 5:9–16.
96. Furr M, Kennedy T. 2001. Cerebrospinal fluid and serum concentrations of ponazuril in horses. *Vet Ther* 2:232–7.
97. Lindsay DS, Dubey JP, Kennedy TJ. 2000. Determination of the activity of ponazuril against

Sarcocystis neurona in cell cultures. *Vet Parasitol* 92:165–9.
98. Kennedy T, Campbell J, Selzer V. 2001. Safety of ponazuril 15% oral paste in horses. *Vet Ther* 2:223–31.
99. Welsh TH, Bryan TM, Johnson L, *et al*. 2002. Characterization of sperm and androgen production by testes from control and ponazuril-treated stallions. *Theriogenology* 58:389–92.
100. Furr M. Unpublished observation.
101. Pharmaceuticals I. 2003. Freedom of information summary. NADA 141-178 NAVIGATOR (32% nitazoxanide). Antiprotozoal oral paste for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.
102. Anon. 2006. Nitazoxanide. In *AHSF Drug Information 2006*, edited by McEvoy GK, 893–5. American Society of Health-System Pharmacists.
103. Fenger CK. 1998. Treatment of equine protozoal myeloencephalitis. *Compend Contin Educ Pract Vet* 20:1154–7.
104. Witonsky S, Morrow JK, Leger C, *et al*. 2004. *Sarcocystis neurona*-specific immunoglobulin G in the serum and cerebrospinal fluid of horses administered *S. neurona* vaccine. *J Vet Intern Med* 18:98–103.
105. Furr M, McKenzie H, Saville WJA, *et al*. 2006. Prophylactic administration of ponazuril reduces clinical signs and delays seroconversion in horses challenged with *Sarcocystis neurona*. *J Parasitol* 92:637–43.

16
Parasitic Infection of the Central Nervous System

Martin Furr

Parasitic infections of the equine central nervous system (CNS) are relatively uncommon; they lead to very severe disease when present however. One author has suggested that *Strongylus vulgaris* is the most commonly involved parasite, but based on the number of reports in the clinical literature, *Halicepholobus gingivalis* appears to be the most common. This may reflect nothing more than a reporting bias, however. Also based on published reports, it would appear that parasitic myeloencephalitis is less common than in previous years. This may be due to more widespread use and greater efficacy of available anthelmintics, but could also reflect reporting bias.

The general features of parasitic infections of the CNS are an acute onset of asymmetric CNS deficits that are progressive. Few successful cases have been reported, as diagnosis is most commonly made by postmortem.

HALICEPHALOBUS (MICRONEMA) GINGIVALIS

Halicephalobus gingivalis is a free-living saprophytic nematode (order Rhabditata and family Rhabditidae) that normally is found in soil, manure, and decaying humus.[1] Some confusion regarding the classification of this parasite has occurred, and it was originally named as a species of *Micronema*. It was subsequently found that *Micronema* was already in use for a fish genus, and it was recommended that the parasite be moved to the genus *Halicephalobus*.[2] More recently, the parasite has been cultured from a mandibular lesion in a horse and studied in more detail, and the authors established *H. gingivalis* as a valid species, with *H. deletrix* considered a synonym.[3]

The parasite was first described in the nasal tumor of a horse[4] and has subsequently been reported to cause a variety of neurologic and non-neurologic infections of the horse. Infections of bone,[5,6] testicles,[7] eye,[7] kidney,[7,8] mammary gland[9] granulomatous skin lesions,[10] and CNS[5–8,11–14] have all been reported. Meningoencephalitis of humans has also been reported.[15,16] The parasite appears to have a wide geographic distribution as infections have been reported in the US, Canada, Scotland, England, and Italy.

Clinical signs of CNS infection with *H. gingivalis* are variable and depend upon the neuroanatomic localization of the parasite within the CNS. In most cases, ataxia is present and may be associated with encephalitic signs, although more focal lesions have been reported. These include a classic case of cauda equina syndrome[12] as well as ocular parasitism which progressed to encephalitis.[17] In many cases, there were non-neurologic signs which were co-incident with or preceded the neurologic signs; these included renal disease, granulomatous masses of the head, nasal discharge and sinusitis, and uveitis.

The large number of reports in which there is an association with masses/swellings on the head would suggest that this is a normal route of infection (i.e., infection of skin lesions, with subsequent migration); however there may also be hematogenous dissemination. Infections have been seen without any signs of swellings or masses, and these cases may represent direct invasion up through the nasopharynx and cribiform plate.

STRONGYLUS VULGARIS

Due to the extensive tissue migration associated with *S. vulgaris* infection, it is perhaps not surprising that

occasional migration through the CNS occurs. When aberrant infection of the CNS occurs, a wide variety of clinical signs can occur which is due to the location of the parasite within the CNS. Two general syndromes have been reported, however—a chronic ataxia and an acute, progressive encephalitis.[18] Clinical signs in the encephalitic form include blindness, dementia, circling, and dysphagia.[19]

One well-reported case of spinal cord verminous migration found a donkey to have an asymmetric hind limb weakness and ataxia localized to the thoracolumbar spinal cord. The clinical signs progressed to involve more anterior regions of the spinal cord over a period of several days, and the donkey was killed. A postmortem found long tortuous lesions extending over several vertebral segments, corresponding to the cranial progression of the parasite in the spinal cord.[20]

Experimental induction of verminous myeloencephalitis via intracarotid injection of fourth- and fifth-stage larvae of *S. vulgaris* resulted in variable neurologic signs in five of eight ponies.[21] Two ponies died acutely. Blindness was frequently observed, as well as hyperesthesia, gait deficits, convulsions, and laryngeal paralysis. Peripheral white blood cell counts did not change following infection. Cerebrospinal fluid (CSF) parameters were inconsistently reported, but CSF white blood cell counts varied from 0 to 1080 cells/μl, and total protein ranged from 31.5 to 175 mg/dl.[21]

It appears from postmortem examinations that damage from migration of *S. vulgaris* can occur and then heal, as evidenced by healed tortuous tracts within the CNS of horses with relatively mild clinical illness.[18] In these reports, however, clinical signs may not have been carefully recorded, and it is unlikely that the CNS damage associated with such infection is benign.

Pathophysiology is believed to involve an embolic shower from parasite-induced granulomas in the heart or ascending aorta, leading to infarction of the CNS. This process may embolize larvae. All six horses in one report had verminous thrombotic masses, supporting this view. Alternatively, individual larvae have been found to enter the spinal cord and migrate.[20]

HYPODERMA (BOVIS AND LINEATUM)

Intracranial myiasis has been reported to be fairly common in the nineteenth century in Europe; however, it has been very uncommonly reported in more recent times.[19,22] Presumably, the widespread and frequent use of anthelmintics and the decreasing practice of housing horses with cattle have diminished the frequency of the condition. Larvae of both *Hypoderma lineatum* and *H. bovis* have been described in the CNS of horses.[22,23] The larvae apparently enter the CNS via large foramina such as the foramen magnum, intervertebral foramina, or optic foramina. Once within the CNS, the migration of the larvae through CNS parenchyma results in inflammation, hemorrhage, and tissue destruction.

Clinical signs that have been reported include a relatively abrupt onset of clinical signs which are usually asymmetric and progressive. Ataxia and muscular weakness, circling, blindness, and seizures have been seen, with a clinical course of 1–15 days.[22,23] There is an apparent predisposition for the brain, as Olander reported the larvae to be in the brain in 15 of 16 cases.[22]

MISCELLANEOUS PARASITES

A single case of nervous system disease resulting from infestation with *Draschia megastoma* has been reported.[24] In this case, an acute onset of asymmetric brainstem disease was described, followed by a 5-week course of improvement, then worsening leading to euthanasia. Larval *D. megastoma* are deposited on moist surfaces of the horse by feeding flies. Ingested larvae reach the stomach where they mature and survive in granulomatous masses, but larvae deposited at other sites may migrate widely, occasionally finding their way to the brain.

Angiostrongylus cantonensis has been described in two foals in Australia.[25] Clinical signs included a "dog-sitting" posture and inability to rise in one, and ataxia followed by recumbency in the other. Treatment of one foal with ivermectin was attempted, yet progression of clinical signs was rapid, and both foals were humanely destroyed due to the severity of their clinical condition. Postmortem examination found meningitis and larval parasite within the CNS with variable degrees of inflammation. Eosinophilic inflammation was a prominent component in one foal.

Normally, *A. cantonensis* is a parasite of rats in which the third- and fourth-stage larvae migrate through the CNS. It is possible to acquire infective larvae by direct ingestion, or by invasion of traumatized skin. The route of infection in these two foals was not determined.

A parasite proposed to be *Parelaphostrongylus tenuis* has been found in one horse associated with a syndrome of acquired dorsal gray matter myelitis and cervical scoliosis.[26] It was proposed that the parasite migrated up spinal nerves into the dorsal gray columns, inducing a unilateral degeneration that results in the clinical signs. Although the dorsal gray column has been identified as a preferred site for the development of *P. tenuis*, the parasite of the report was not conclusively identified and was not found in the other five horses of the study with cervical scoliosis. Hence, it is premature to suppose that cervical scoliosis is due to parasitic migration, but it clearly demonstrates that it can cause this presentation in at least some cases.

DIAGNOSIS

Antemortem diagnosis of verminous myeloencephalitis is difficult. There is little about the anamnesis or clinical signs that are unique in such cases. Horses with *Halicephalobus*-induced myeloencephalitis may have signs of kidney disease, or granulomatous swellings of the skin or head; those with *Hypoderma* infections may have skin warbles. Most horses have a history of abrupt onset of asymmetric CNS disease which is usually progressive. Differential considerations include trauma, bacterial, viral, fungal, or protozoan infections. If seizures or abnormal behaviors are present, then leukoencephalomalacia should be considered.

Routine serum chemistry analysis and complete blood count (CBC) are unlikely to be altered in cases of verminous myeloencephalitis. Nonspecific changes in the serum biochemistry analysis, such as dehydration or increased muscle enzyme activity, may exist secondary to recumbency or an inability to drink and maintain hydration. A stress leukogram may be seen in animals that are anxious and distressed.

The most rewarding diagnostic test is probably the CSF evaluation. The nature of the changes in the CSF is likely to be dependent upon the number and size of organisms, as well as the on duration of clinical disease and collection site. Nonspecific signs of inflammation are often present, and an eosinophilic pleocytosis is expected but is not commonly reported. In a horse with severe CNS disease from *D. megastoma*, the lumbosacral CSF was described as "normal,"[24] while in a horse with *S. labiatopapillosa*, the CSF was originally described as normal, then was found upon repeat analysis a few days later to be mildly xanthochromic and to have an increased nucleated cell count and total protein.[27] Changes in the CSF of two horses with *H. gingivalis* infection included a mild xanthochromia and normal to mildly increased total protein (69 and 81 mg/dl).[13] A mild pleocytosis (25 and 81 nucleated cells/μl) was observed in both horses, but eosinophils were only observed in one case (1 eosinophil/μl).[13] Lymphocytes predominated in both cases.[13] In another case, there was a marked CSF pleocytosis (2030 cells/μl) of which "only a few" were eosinophils.[6] Nucleated cell counts appear to vary dramatically, and neutrophils and mononuclear cells predominate.[21] It would appear from these results that mild elevations of total protein and cell count, along with evidence of hemorrhage (as xanthochromia), are consistent with verminous myeloencephalitis. Neutrophilia is common, and eosinophilia is uncommon in most cases, with the notable exception of the high eosinophil count in the *A. cantonensis* case.

In some cases, larvae may be seen in CSF.[19] When present, these provide a high degree of confidence in the diagnosis. This is most likely to occur in cases of *Halicephalobus* and is unlikely in cases of *S. vulgaris* or larval myiasis, due to the size of the parasite.

Just as it is hard to confirm verminous encephalitis antemortem, it is equally difficult to rule it out; hence, it may be prudent to assume that it is present, and treat for it, if CSF findings are consistent and no other etiology is determined (Table 16.1).

TREATMENT

Treatment of verminous myeloencephalitis has not been documented in the literature to have much success; however, as it is so difficult to confirm verminous myeloencephalitis antemortem, the true incidence of successful treatment is unknown. Most modern anthelmintics have efficacy against the parasites reported to cause verminous encephalitis; however, their ability to achieve effective concentration in the CNS and CSF is unknown. The amount of tissue necrosis and inflammation produced by most large parasites is such that local (CSF and CNS) concentrations in the area of the infection are probably high. It is probably best to use antiparasitic agents that provide a rapid kill to minimize the progression of damage. Combinations of fenbendazole and ivermectin are reasonable, and ivermectin

Table 16.1. Cerebrospinal Fluid Results in Various Cases of Equine Verminous Myeloencephalitis

Xanthochromia	Nucleated Cell Count	Neutrophil Cells	Macrophage Cells	Lymphocyte Cells	Eosinophil Cells	Total Protein	Organism
NEG	2.03×10^9/l	Mostly			Few	0.89 g/dl	*Halicepholobus*[6]
	60 cells/μl					710 mg/dl	*Halicepholobus*[12]
2+	81 cells/μl	8/μl	40/μl	33/μl	0	114 mg/dl	*Halicepholobus*[27]
	25 cells/μl	4/μl	6/μl	14/μl	1/μl	69 mg/dl	*Halicepholobus*[27]
Mild	9988 cells/μl	7191/μl	1199/μl	1398/μl	200/μl	550 mg/dl	*S. vulgaris*[20]
Mild	Increased					Increased	*Setaria*[26]
	1563×10^6/l	18×10^6/l	219×10^6/l	120×10^6/l	1206×10^6/l		*Angiostrongylus*[25]
Not reported	35 cells/μl	9/μl	20/μl		6/μl	100 mg/dl	*Halicepholobus*[34]

Normal values are 0.005×10^9/l or <5 cells/μl, and 0.7 g/dl or <90 mg/dl.

should probably not be used alone, due to its "slow-kill' action and questionable penetration of the blood–brain barrier (BBB). It has been suggested that treatment may result in an acute worsening of the clinical signs due to inflammation associated with parasite death; however, there is no objective information available to support this position. Clearly, if parasite is present within the CNS, anthelmintic treatment is required and control of associated inflammation is important (Table 16.2).

The use of antiinflammatory drugs for CNS disease is discussed in detail in Section 1, Chapter 4; however, a general course of treatment would involve the use of intravenous dimethyl sulfoxide (DMSO), nonsteroidal antiinflammatory drugs, and corticosteroids.

TRYPANOSOMA INFECTIONS

The hemoflagellate protozoa of the genus *Trypanosoma* are pathogenic to horses, resulting in a variety of clinical disorders, including meningoencephalitis. *Trypanosoma evansi* is the causative agent of "Surra," while *T. equiperdum* causes "Dourine." While no longer present in North America, these are important pathogens in many parts of the world.

Surra is an important disease affecting horses, mules, and camels in North Africa, the Middle East, Asia, Indonesia and the Phillipines, and Central and South America.[28] The organism is transmitted host to host, mechanically from the mouth parts of the biting flies *Tabanus* and *Stomoxys*; transmission is enhanced by high-density housing of horses and during periods of high insect population (i.e., during the wet season).[28] An incubation period of 1–2 weeks follows, after which time, there are large numbers of parasites present in the blood, but only transiently. Parasitemia is associated with fever and progressive anemia, ventral edema, weight loss, and the development of CNS abnormalities.[28,29] Neurologic signs appear to be variable, with generalized weakness and progressive hindlimb paralysis, as well as restlessness and circling.[28,30]

Diagnosis of Surra is accomplished by observation of the clinical syndrome in a known endemic area. Diagnostic aids include direct observation of trypanosomes in blood or tissue fluids; however, parasitemia may be transitory. Mouse inoculation tests may also be performed,[30] and an indirect ELISA test has been described.[30] The mouse inoculation test is considered the most sensitive technique,[30] while the ELISA test had a low sensitivity but was considered useful for screening.[30]

Pathologic findings in horses with Surra demonstrated nonspecific changes including emaciation, subcutaneous and ventral edema, and enlarged lymph nodes. Histologically, there is a generalized nonsuppurative meningoencephalitis affecting both white and gray matter of the brain. Extensive lymphocytic/plasmacytic perivascular cuffing was seen, and neuronal necrosis was not considered a prominent feature.[29]

Treatment of Surra is commonly attempted with suramin at a dose of 10 mg/kg body weight IV, then repeated in 1 week.[28] Other drugs that can be used include isometamidium chloride (Samorin, Rhone Merieux) at 0.25–2 mg/kg body weight IM. Phenylarsonate (Cymelarsen, Rhone Merieux) is effective against resistant strains of *T. evansi*, but it has not been evaluated in the horse.[28] Dimenazine at 3.5 mg/kg body weight has been used; however, resistance may be widespread and it was ineffective, and associated with toxicity, in a group of horses and mules in Thailand.[30]

Dourine, caused by *T. equiperdum*, has a very extensive geographic range; however, it is not restricted by climate and due to the movement of breeding animals internationally could be seen worldwide. Dourine is a venereal disease that results primarily in local infection of the genitalia, with swelling, edema, and discharge. Skin ulcerations may also occur, and fever is sporadic.[28] Neurologic signs may occur later in the infection, and horses demonstrate ataxia and stumbling, with muscle spasms of the hindquarters and facial

Table 16.2. Anthelmintics of Potential Value in Cases of Verminous Myelencephalitis[19,24]

Drug	Dose
Fenbendazole	60 mg/kg once
Fenbendazole	50 mg/kg once per day for 2–3 days
Thiabendazole	440 mg/kg once
Diethyl carbamazine (DEC)	50–100 mg/kg repeated in 3 days
Trichlorfon	40 mg/kg

paralysis.[28] Nervous system involvement is described as invariably fatal.[28]

The neurologic signs are reported to occur coincident with the presence of trypanosmes in the CSF; hence observation of organism from CSF would be confirmatory.

SETARIA (KUMRI)

Infection of the CNS with *Setaria* spp. (Nematoda: Filarioidea) appears to be a fairly common illness in Central and Southeast Asia, resulting in a condition referred to colloquially as "Kumri"—meaning "weak back" in Hindustani.[31] The illness has been described in India and China by British veterinarians beginning in the late 1800s and is due to CNS infestation with *Setaria digitata*.[32] A closely related species, *Setaria labiatopapillosa*, has been described in a single horse in the United States.[27] There are apparently regional differences in incidence in which disease is more common in low-lying areas with high seasonal rainfall.[31]

Clinical signs observed from either parasite appear to be similar, and spinal ataxia with posterior weakness predominates. Signs of involvement of the cauda equina were reported in one horse,[27] and cerebral lesions were noted in two horses in Japan.[33] Fever or other systemic signs of illness are not apparent, and clinical signs from infection of non-nervous tissue are limited to the wonderfully descriptive "worm-in-the-eye" as quoted by Innes, 1952, from "Hippopathology, Vol. III (1843)." That this illness could indeed be due to *Setaria* spp. is supported by a report of a *Setaria* spp. surgically recovered from the eye of a horse with uveitis.[34] Neurologic signs appear in most cases to be abrupt in onset and progressive, although historical accounts describe variability in the severity and rapidity of progression.[32]

Few detailed reports of pathologic changes can be found; however single or multifocal areas of inflammation with hemorrhage and necrosis have been described.[27,32,33] One report described tract-like lesions as well as individual random foci of necrosis.[27] Parasite cross-sections may be seen.

REFERENCES

1. Bowman DD. 1999. Helminths. In *Georgis' Parasitology for Veterinarians*, edited by Bowman DD, 109–234. Philadelphia: W.B. Saunders Co.
2. Andrassy L. 1973. Uber vier homonyme Nematodengathungen. *Nemathologia* 19:403–4.
3. Anderson RC, Linder KE, Peregrine AS. 1998. *Halicepholobus gingivalis* (Stefanski, 1954) from a fatal infection in a horse in Ontario, Canada with comments on the validity of *H. deletrix* and a review of the genus. *Parasitology* 5:255–61.
4. Anderson RV, Bemrick WJ. 1965. *Micronema deletrix* n. sp. a saprophagus nematode inhabiting a nasal tumour of the horse. *Proc Helminth Soc Wash* 32:74–5.
5. Keg PR, Mirck MH, Dik KJ, *et al*. 1984. *Micronema deletrix* infection in a Shetland pony stallion. *Equine Vet J* 16:471–5.
6. Brojer JT, Parsons DA, Linder KE, *et al*. 2000. *Halicephalobus gingivalis* encephalomyelitis in a horse. *Can Vet J* 41:559–61.
7. Kinde H, Mathews M, Ash L, *et al*. 2000. *Halicephalobus gingivalis (H. deletrix)* infection in two horses in southern California. *J Vet Diagn Invest* 12:162–5.
8. Blunden AS, Khalil LF, Webbon PM. 1987. *Halicephalobus deletrix* infection in a horse. *Equine Vet J* 19:255–60.
9. Greiner EC, Calderwood-Mays MB, Smart GC. 1991. Verminous mastitis in a mare caused by a free living nematode. *J Parasitol* 77:320–2.
10. Johnson KH, Johnson DW. 1966. Granulomas associated with *Micronema deletrix* in the maxillae of a horse. *J Am Vet Med Assoc* 149:155–9.
11. Stone WM, Stewart TB, Peckham JC. 1970. *Micronema deletrix* Anderson and Bemrick, 1965 in the central nervous system of a pony. *J Parasitol* 56:986–7.
12. Johnson JS, Hibler CP, Tillotson KM, *et al*. 2001. Radiculomeningomyelitis due to *Halicephalobus gingivalis* in a horse. *Vet Pathol* 38:559–61.
13. Darian BJ, Belknap J, Nietfeld J. 1988. Cerebrospinal fluid changes in two horses with central nervous system nematodiasis (*Micronema deletrix*). *J Vet Intern Med* 2:201–5.
14. Cantile C, Rossi G, Braca G, *et al*. 1997. A horse with *Halicepholobus deletrix* encephalitis in Italy. *Eur J Vet Pathol* 3:29–33.
15. Hoogstraten J, Young WG. 1975. Meningo-encephali-myelitis due to the saprophagus nematode, *Micronema deletrix*. *J Can Sci Neurol* 2:121–6.
16. Shadduck JA, Kebelacker DJ, van Telford Q. 1979. *Micronema deletrix* meningo-encephalitis in an adult man. *Am J Clin Pathol* 72:640–3.
17. Rames DS, Miller DK, Barthel R, *et al*. 1995. Ocular *Halicepholobus* (syn. *Micronema*) *deletrix* in a horse. *Vet Pathol* 32:540–2.

18. Little PB. 1972. Cerebrospinal nematodiasis of equidae. *J Am Vet Med Assoc* 160:1407–13.
19. Lester GD. 1992. Parasitic encephalomyelitis in horses. *Compend Contin Educ Pract Vet* 14: 1624–30.
20. Mayhew IG, Brewer BD, Reinhard MK, *et al*. 1984. Verminous (*Strongylus vulgaris*) myelitis in a donkey. *Cornell Vet* 74:30–7.
21. Little PB, Lwin US, Fretz PB. 1974. Verminous encephalitis of horses: experimental induction with *Strongylus vulgaris* larvae. *Am J Vet Res* 35: 1501–10.
22. Olander HJ. 1967. The migration of *Hypoderma lineatum* in the brain of a horse. *Vet Pathol* 4: 477–83.
23. Hadlow WJ, Ward JK, Krinsky WL. 1977. Intracranial myiasis by *Hypoderma bovis* (Linnaeus) in a horse. *Cornell Vet* 67:272–81.
24. Mayhew IG, Lichtenfels JR, Greiner EC, *et al*. 1982. Migration of a spiruroid nematode through the brain of a horse. *J Am Vet Med Assoc* 180:1306–11.
25. Wright JD, Kelly WR, Wadell AH, *et al*. 1990. Equine neural angiostrongylosis. *Aust Vet J* 68: 58–60.
26. van Biervliet J, De Lahunta A, Ennulat D, *et al*. 2003. Acquired cervical scoliosis in six horses associated with dorsal grey column chronic myelitis. *Equine Vet J* 35:86–92.
27. Frauenfelder HC, Kazacos KR, Lichtenfels JR. 1980. Cerebrospinal nematodiasis caused by a filariid in a horse. *J Am Vet Med Assoc* 177: 359–62.
28. Luckins AG. 1994. Equine trypanosomiasis. *Equine Vet Educ* 6:259–62.
29. Seiler RJ, Omar S, Jackson ARB. 1981. Meningoencephalitis in naturally occurring *Trypanosoma evansi* infection (Surra) of horses. *Vet Pathol* 18:120–2.
30. Tuntasuvan D, Jarabrum W, Viseshakul N, *et al*. 2003. Chemotherapy of surra in horses and mules with diminazene aceturate. *Vet Parasitol* 110: 227–33.
31. Innes JRM, Pillai CP. 1955. Kumri-so-called lumbar paralysis of horses in Ceylon (India and Burma), and its identification with cerebrospinal nematodiasis. *Br Vet J* 3:223–35.
32. Innes JRM. 1952. Cerebrospinal nematodiasis: a nervous disease of animals caused by immature nematodes (*Setaria digitata*) and its relationship to Kumri of horses in India. *Indian Vet J* 29:81–6.
33. Yoshihara T, Oikawa M, Kanemaru T, *et al*. 1987. Two cases of cerebrospinal setariosis in the race-horses. *Bull Equine Res Inst* 24:14–22.
34. Jemelka ED. 1976. Removal of *Setaria digitata* from the anterior chamber of the equine eye. *VM SAC Vet Med Small Anim Clin* May:673-5.

17
Clostridial Neurotoxins: Botulism and Tetanus

Martin Furr

Neurologic disease resulting from infection with clostridial organisms is not common, but is severe when it occurs. The clostridial neurotoxins are some of the most potent biological toxins known, leading to the clinical conditions of botulism (a flaccid paralysis) and tetanus (a tetanic paralysis). Both toxins exert their effects by inhibiting neurotransmitter release, but the anatomic localization of the inhibition results in the markedly different clinical signs. For the clostridial neurotoxins to alter neurotransmitter release, they must bind to and be internalized into the nerve terminal. The toxins first bind to large negatively charged molecules (polysialogangliosides) on the nerve terminal. After this, the ganglioside/toxin complex binds to a second specific protein receptor on the nerve terminus surface. The specific nature of this receptor is believed to determine the subsequent internalization and differential localization of the toxins within the nerve. After internalization into the nerve terminal, tetanus toxin migrates retrograde along the motor neuron to the spinal cord and brainstem. Botulism toxin remains at the nerve terminus of the neuromuscular junction (NMJ).

Once the cell body is reached, tetanus toxin is moved by transynaptic exchange into the terminal of inhibitory motor neurons of the spinal cord. Tetanus toxin cleaves VAMP (synaptobrevin), a "docking protein" required for exocytosis of neurotransmitter, which in the spinal inhibitory interneuron is glycine and γ-aminobutyric acid (GABA).[1–3] In contrast, botulinum toxin remains within the nerve terminus of the NMJ and blocks acetylcholine release by attacking proteins responsible for neurotransmitter exocytosis at the NMJ. Specifically, botulism toxin types A and E cleave SNAP-25, serotypes B, D, F, and G inactivate VAMP (synaptobrevin), and serotype C inactivates syntaxin (Figure 17.1; Table 17.1).[3]

TETANUS

Tetanus is a neurologic disease resulting from the toxin of *Clostridium tetani*. *C. tetani* is a Gram-positive, obligate anaerobic bacillus. Occasionally, it forms long filaments in culture.[4] The organism exists primarily in spore form and is common in the gastrointestinal (GI) tract of animals and subsequently is a common soil organism. Spores are highly resistant to environmental extremes and antimicrobials, but can be destroyed by heating to 239°F (115°C) for 20 min.[4] *C. tetani* produces three toxins: (1) tetanospasmin (neurotoxin), (2) hemolysin, and (3) a peripherally acting nonspasmogenic toxin. Tetanospasmin is responsible for the characteristic clinical features of tetanus, and antibodies to this toxin are protective.[4]

Neurologic disease is seen following infection of wounds with *C. tetani* spores. Clostridial growth occurs in conditions of a low O_2 tension; hence deep penetrating wounds are common sources of infection. Wounds with a large amount of tissue necrosis or impaired blood supply can also provide a favorable environment for growth of the organism. Tetanus has been observed following castration, metritis, retained placenta, and injection abscesses in adult horses.[5] In a case series of 20 horses with tetanus, puncture wounds to the distal limbs were the most common wound history, with lacerations and sole abscesses being very common, and wounds to the head also reported but infrequently.[6] The

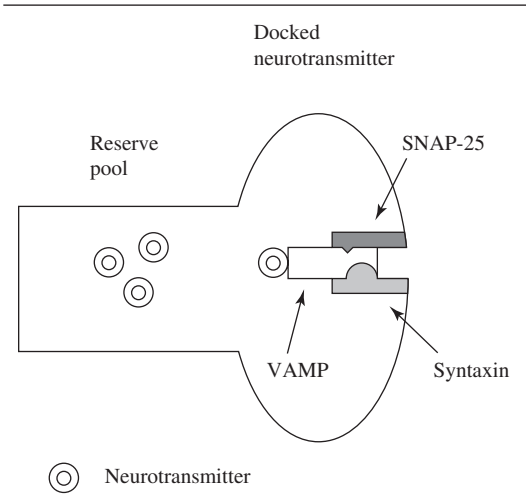


Figure 17.1. Schematic demonstrating the relationship of botulinum toxins at the motor end plate.

Table 17.1. Clostridial Neurotoxins and their Target Proteins

Toxin	Target
Tetanus toxin	VAMP (synaptobrevin)
Botulinum toxin	
A	SNAP-25
B	VAMP (synaptobrevin)
C	SNAP-25 and syntaxin
D	VAMP (synaptobrevin)
E	SNAP-25
F	VAMP (synaptobrevin)
G	VAMP (synaptobrevin)

umbilicus has been implicated as a site of infection in neonates.[5] The time from wound occurrence until development of neurologic signs can vary greatly, with the average reported in one case series to be 9 days, with a range of 2–21 days.[6] Other authors have stated that clinical signs may occur months after the injury, due to prolonged viability of spores in tissues.[5]

Clinical Signs

The clinical signs of tetanus observed in horses are due to the effects of the neurotoxin on striated and smooth muscles. Examination reveals a diffuse, symmetrical hypertonicity and hyperresponsiveness of all muscle groups. The severity and rate of progression of clinical signs vary depending upon the dose of neurotoxin and the size, age, and immune status of the infected animal. Initial signs observed may reflect the location of the injury, but in almost all cases progress rapidly to a diffuse, symmetrical tetanic spasm of muscles. The most common clinical signs are hyperesthesia and prolapse of the third eyelid, both of which were seen in 85% of cases.[6]

Early signs include reluctance or inability to feed off the ground due to spasm of the neck muscles, a mildly stiff gait, or hyperresponsiveness to external stimuli such as sound or unexpected motion (exaggerated "startle" response). Contraction of the facial muscles results in an "anxious" expression with retracted lips, flared nostrils, and erect ears (risus sardonicus). Prolapse of the nictitating membrane is seen due to retraction of the globe. Prolapse of the nictitating membrane can be accentuated ("flick of the haw") by tapping on the forehead or making a sudden noise. Progressive tetany of skeletal muscles results in a stiff gait, with rigid extension of the neck and limbs, resulting in the classic "sawhorse" stance. Spasms of muscles may result in a ventral or lateral arching of the neck or back. Dysphagia may occur due to involvement of the muscles of mastication and swallowing, and retention of feces and urine can occur. Spasm of the muscles of mastication (trismus) and elevation of the tail head are also commonly seen.

The tetanus toxin also affects the autonomic system, and in humans labile hypertension and tachycardia are commonly seen.[7,8] Tachycardia is commonly seen in horses with tetanus; however, it is difficult to conclusively state if this is due to the direct action of the toxin on the autonomic nervous system, or rather a response to the discomfort, anxiety, and struggling that the horse may experience when afflicted with tetanus.

As the severity of the tetany progresses, horses usually become recumbent. Efforts to stand result in clonic/tonic spasms, which may be confused with convulsions. In this case, however, the horse remains conscious of its surroundings and responds to external stimuli—this is not observed in horses with seizures. Prolonged and uninhibited muscle contraction can result in fracture of long bones, and self-induced trauma during this activity can be severe.

Death usually occurs due to paralysis of respiratory muscles and is seen within 5–7 days of the initial clinical signs. Bloating associated with GI stasis may result in colic and/or respiratory embarrassment. Complications such as aspiration pneumonia, rhabdomyolysis, and subsequent renal disease can be seen and may be severe and fatal. The reported mortality rate is high (up to 75%) and is highly dependent upon prior immunization status.[6] Those horses that had been vaccinated within 1 year of the intoxication had a significantly higher survival rate.

Treatment

Treatment of tetanus in the adult horse is a considerable challenge, and the general principles of treatment are (1) destruction of *C. tetani* organism, (2) neutralization of unbound toxin, and (3) control of muscle spasms. In addition, good nursing care is of particular importance in overall response.

Destruction of the organism is achieved most commonly with the use of appropriate antibiotics, combined with wound debridement if possible. Historically, penicillin has been recommended in the veterinary literature at various dosages up to 50,000 IU/kg for the first 2 days of treatment.[5] The chemical structure of penicillin is similar to GABA, an important inhibitory neurotransmitter, and penicillin may act as a competitive antagonist.[7] High doses of penicillin may therefore synergize with tetanus toxin to block GABA activity and worsen clinical signs. Recent comparative studies in human tetanus have demonstrated metronidazole to be superior to penicillin and is the preferred antimicrobial.[7] Other antibiotics of value include erythromycin, doxycycline, and chloramphenicol. If the wound cannot be adequately debrided, then increasing the antimicrobial dosage is a reasonable course of action. Antimicrobial treatment should be continued for at least 10 days, the ultimate goal being to ensure the death of the spore form of the bacteria in tissues. The value of hyperbaric oxygen therapy in horses with tetanus (to aid clearance of the organism) is unknown, but may be considered.

Neutralization of toxin is achieved by treatment with tetanus antitoxin (TAT), in most cases given either intravenously or intramuscularly. TAT will neutralize only circulating toxin, however, and has no effect upon toxin which has entered the nervous system or is within neurons. Recommended dosages of TAT vary widely, and the optimum dose is not known. Doses of TAT as high as 2.5 million IU (once) or 220 IU/kg q 12 h have been suggested by some authors. Others have suggested that a dose of 5–10,000 IU is probably adequate, as the amount of circulating toxin is usually very low. One study suggests that daily treatment with TAT (2500 IU subcutaneously for 3 days) following an initial dose had better outcomes.[6] In those horses in which adequate wound debridement cannot be obtained, or in which clinical signs have been present for more than 1 day, higher dosages of TAT are justified. It is important that TAT be given before aggressive wound debridement occurs, as a release of toxin may occur during or following this procedure.

An alternative means of neutralizing tetanus toxin is via intrathecal (subarachnoid) administration of TAT. This means of delivery bypasses the blood–cerebrospinal fluid (CSF) barrier and allows at least some unbound toxin to be neutralized. In one study, this mode of treatment was considered to result in a rapid halt of the progression of the clinical signs, with a survival of 77%, as compared with a survival of 50% in historical controls.[9] Using intrathecal therapy with TAT, the progression of signs was halted, but not reversed; hence this therapy is obviously most beneficial early in the course of illness. If clinical signs are allowed to progress, and intrathecal TAT is considered a treatment of last resort, then results are likely to be poor. In another study, five horses treated with intrathecal TAT did not survive. In addition, this treatment is not without potential complications as seizures were reported in one of the five horses following intrathecal TAT.[6] Horses treated with intrathecal TAT in this study were very severely affected prior to the treatment, however. The risks of anesthesia must be considered if the atlanto-occipital (AO) site is used.

Intrathecal administration of TAT can be performed at either the AO or lumbosacral site, and there is no clear benefit of one site over the other. AO administration requires general anesthesia; however, the bulk flow of CSF from a cranial to caudal direction may ensure the most opportunity for toxin–antitoxin interaction. Five to 10,000 IU of TAT is slowly administered after removal of an equal volume of CSF. The concomitant use of 20–100 mg prednisolone sodium succinate has been advocated to minimize meningeal inflammation, but is an unproven adjunctive therapy.

In addition to TAT, it is important to provide active immunization using tetanus toxoid at the earliest opportunity. This should be administered at standard dosages, and at a site distant from the injection site from the TAT to minimize interaction. Naturally occurring infection does not appear to result in protection against future disease.

Control of muscle spasms is often difficult in horses with tetanus, but is important in the overall success of management. The ideal drug or drug combination has not been determined, but a number of options exist. Centrally acting muscle relaxants, such as methocarbamol and glycerol guaicolate, are probably the best choice as they block polysynaptic reflex activity in the brainstem and spinal cord. Methocarbamol (10–20 mg/kg q 8 h) is relatively inexpensive and efficacious in mild cases. Glycerol guaiacolate has a very short duration of action, and horses with tetanus given this drug often go down, but it has been suggested that it can be used by slow continuous infusion, titrated to effect. Diazepam reduces anxiety and muscle spasms by potentiating the release of GABA and has been proven beneficial in humans with severe tetanus.[10,11] It is quite useful in horses with tetanus, particularly when combined with alpha-2 agonists such as xylazine.[6] Chlorpromazine or acepromazine are probably the most commonly employed and are useful in mild cases, but are often ineffective in more severe cases.

On an interesting historical note, one of the earliest reported drugs for the treatment of tetanus in the horse was curare, which was reported to be used in two horses with tetanus in 1835, as reported by Smithcors (1956).[12] Several other historical attempts were described by Smithcors, and though the initial beneficial clinical effects of the curare were apparently quiet remarkable, all the horses died within a few hours.[12]

Overall management of horses with tetanus is very important in the overall outcome of the case. Horse which cannot eat or drink should be appropriately supported using an indwelling nasogastric tube, or intravenously. Repeated passage of a nasogatric tube should be minimized due to the risk of aspiration pneumonia in a dysphagic horse, and intravenous fluids may be optimal. Manual evacuation of the bladder and rectum may be necessary. Horses can be aided to remain standing by use of a sling if they will tolerate it, and they should be maintained in a quiet, darkened stall with minimal stimulation. Horses that are recumbent have a very poor prognosis, and early euthanasia should be considered.

Diagnosis

There is no specific antemortem test for the diagnosis of tetanus in the horse. The clinical signs are quite characteristic; however, given the very low prevalence of this disease in most horse rearing areas, it is often "forgotten" as a possibility. Clinical signs of diffuse, symmetrical muscle tetany, prolapsed nictitating membranes, and history of recent wound or trauma provide strong evidence for tetanus. The clinical signs could be confused with azoturia/exertional rhabdomyolysis; however, the clinical history would in most cases be revealing. Hypomagnesemia can result in muscle fasciculations, tetany, and risus sardonicus. This can be ruled out with an assay of serum magnesium. Poisoning with strychnine will also result in very similar clinical signs. As noted above, in horses that are recumbent, tetanic paddling can resemble seizure activity, and this possibility should be ruled out by careful neurologic examination.

Clinical chemistry evaluation is often unremarkable in horses with tetanus, or may reflect nonspecific changes of infection, dehydration, or increased muscle activity from muscle spasms and recumbency. Electromyography will reflect prolonged insertional activity, and nerve conduction velocities are normal. CSF evaluation is unremarkable. Serum antibody titers for *C. tetani* may be performed but are unlikely to add significant diagnostic value during the clinical phase of the disease.

Postmortem examination reveals no findings specific to tetanus. Signs of recumbency may be seen, as well as evidence of a penetrating, infected wound. Culture of infected tracts and confirmation of the presence of *C. tetani* by appropriate microbiological methods would support the final diagnosis. Smears made from infected wounds will demonstrate the characteristic "badminton racket" or "drumstick" appearance. Presence of toxin can be confirmed by homogenizing tissue and treating with 50% ethanol for 1 h. The homogenate is then centrifuged and the 0.2 ml of supernate injected into the muscle of naïve and antitoxin-treated mice. Clinical signs of tetanus, or death, will be observed in the unprotected mice within 3 days.[4]

Prophylaxis

The control of tetanus is readily achieved by active immunization with any number of commercially available vaccines. Most require an initial vaccine series, followed by annual revaccination. Vaccinated horses with injuries and deep wounds, or those undergoing elective surgical procedures, should be boostered. Vaccine titers probably last up to at least 4 years following a booster.[13] In a review of 20 cases, however, horses that had been vaccinated within 1 year of the illness had a better prognosis than those which had not been vaccinated within 1 year of the wound.[6] This suggests that antibody titers had declined to suboptimal concentrations.

Unvaccinated horses, or those in which the vaccination history is unknown, should receive 1500 IU of TAT following injury, or before emergency surgery. Tetanus toxoid should be administered at the same time, at a separate site from the TAT, then boostered if the horse is unvaccinated. There is an association of acute hepatic necrosis (Theiler's disease) following TAT; however, this should not be an argument against the use of TAT in those circumstances.

Pregnant mares that were vaccinated in the last month of pregnancy generally provide adequate passive immunity to tetanus in colostrum, which may last up to 3 months of age. Hence, it is reasonable to begin tetanus prophylaxis at 3 months of age. In addition, TAT (1500 IU, intramuscular) can be given to foals at birth if there is any question regarding the mare's vaccination status or the foal's consumption of colostrum. It has been recommended that foals should be given toxoid at 3, 4, and 6 months of age, then annually thereafter.[6]

BOTULISM

Botulism is caused by intoxication with the exotoxin of *C. botulinum*. The organism was recovered from the soil in 18.5% of soil samples tested in the US. *C. botulinum* produces several different subtypes of toxin, which are identified as types A, B, C, C_1, C_2, D, E, and F. The distribution of the different toxin subtypes varies, however, with type A found west of the US Rocky Mountains and type C found most commonly in Europe. Some cases of equine botulism from type C, however, have been reported from Florida, California, New England, Arizona, and Canada.[14–17] Type C botulism has also been reported in Australia.[18] Type B toxin is most commonly found in the Mid-Atlantic region of the US, and Kentucky, and is the most commonly reported cause of botulism in the US (>85%).[19] Type B botulism seems to be most commonly associated with silage, while type C appears to be more commonly seen when forage is contaminated with carcasses. Type D botulism is rare in the horse but was suspected in one outbreak of botulism in horses in California.[20] The use of round bale hay has also been incriminated as a risk factor for botulism in horses, and storing the bales in plastic bags appears to increase the risk.[21,22] Apparently, the common practice of storing such hay outdoors, where it can became wet, leads to proper conditions for the growth of *C. botulinum*. Any form of wet hay however, even small square bales, can be a source of botulism toxin.[23]

Like other organism of the genus *Clostridium*, *C. botulinum* forms spores that withstand extremes of temperature and humidity, and that vegetate and grow under anaerobic conditions, and an alkaline or neutral pH (pH >4.5). Once the organism begins to grow, the toxin is elaborated. Sporulation, replication, and toxin elaboration cannot occur in an acidic environment (pH <6); hence poorly made silage has been a source of intoxication.[24,25] The increased incidence of botulism in Europe has been proposed to be associated with the increased use of grass silage, in many cases associated with type B botulism.[26,27]

Pathophysiology

There are three major mechanisms by which intoxication occurs in equine botulism. Ingestion of preformed toxin ("forage poisoning") from the environment is probably the most common source of intoxication in adult horses. A second source is elaboration of toxin from *C. botulinum* infection in wounds (wound botulism), such as castration sites.[28] One case of wound botulism was associated with an injection site abscess,[29] and infection of umbilical remnants of foals is also considered wound botulism. A final mechanism is the ingestion of *C. botulinum* spores, which then vegetate and produce toxin within the GI tract (toxicoinfectious botulism).[30,31] This is usually attributed to type B toxin.[19] It has been proposed that inflammatory sites within the GI tract, such as gastric ulcers, may be sites for toxin production, yet this hypothesis remains unproven.[31]

Clinical Signs

The clinical signs of botulism are fundamentally derived from a consideration of the pathophysiology of the disorder. The botulism toxin results in a diffuse, flaccid paralysis and loss of muscle strength. Clinical abnormalities are symmetrical, which is an important observation in evaluating such cases. All aspects of the clinical examination findings reflect this fact. The clinical signs are the same regardless of the mechanism of infection; however, it has been proposed that there may be subtle differences in clinical signs depending upon the various toxin types.[19] This remains unconfirmed at the present time.

Clinical signs can be seen at any time from 12 h to 10 days following ingestion of the toxin.[19] Initial signs often include subtle signs of dysphagia or muscular weakness or horses may be found dead. The severity of clinical signs and the rapidity of progression depend upon the amount of toxin ingested. Early clinical signs that may be seen include generalized muscle weakness leading to a lowered head carriage, slow eating, and a shuffling gait with toe dragging. Colic has been the initial presenting complaint in some reports.[16,19]

Constitutional signs are usually normal, although mild dehydration may be seen as the condition progresses and horses are unable to drink. Tachycardia may be seen in horses that struggle to stand, but heart rate is normal early in the course of the disease. Constipation, urine dribbling, or bladder distention may be seen. In more severe cases, an exaggerated respiratory effort, associated with a normal or reduced respiratory rate, may be seen. Aspiration pneumonia may be present.

A thorough neurologic examination will reveal mydriasis and ptosis generally early in the clinical course of the illness. A slow papillary light reflex may be seen, but often is difficult to assess and equivocal. Tail tone is often diminished in clinical cases; however, it has been reported to be variable in experimental induction of the disease.[32] Muscle trembling and fasciculations of large muscle groups may be seen. Tongue tone is diminished and delayed retraction is commonly seen. Horses normally retract the tongue very quickly; horses with botulism will withdraw the tongue slowly and with difficulty and may be unable to do so. Dysphagia is commonly observed and can be tested by the horse's ability to swallow a stomach tube. In addition, prolonged time to consume a standard amount of grain has been used in experimental cases and was considered a good means to evaluate dysphagia. Normal horses were found to consume a 250 ml cup of grain in less than 2 min, while horses with experimentally induced botulism ate much more slowly, and with greater difficulty.[32] The value of this test in clinical cases is not clearly established. Adult horses can be seen to immerse their entire muzzle under water to drink, and nursing foals will spill milk when nursing. These signs may be seen in other causes of dysphagia and are not specific to botulism.

Horses are weak but are not ataxic. Proprioceptive deficits are not present, but horses may be too weak to properly position the limb. Careful observation is required to differentiate between the two. Stumbling and tripping is often seen, as horses do not pick their feet up when walking. This leads to a shuffling, slow gait. The head is typically held lower than normal, and in severe cases may lead to head edema and respiratory stridor.

In foals, the clinical signs above can also be seen, but more commonly foals present with a history of excessive recumbency and muscle fasciculations ("shaker foal syndrome"). Foals are typically bright and alert when down—usually in a normal, sternal position. They may stand and appear to be normal for several minutes, then are observed to demonstrate diffuse fine muscle fasciculations which progress to coarse muscle trembling, then stumbling followed by recumbency. When lying down, the muscle fasciculations cease, and the foal looks normal once again. This cycle may be repeated several times, or may progress rapidly to complete recumbency rapidly, depending upon the dose of toxin acquired and the time since intoxication.

Diagnosis

A presumptive diagnosis of botulism is based on history and physical examination findings. An abrupt onset of diffuse, symmetrical weakness in a horse with normal mentation and the absence of central nervous system (CNS) abnormalities support the diagnosis. Ancillary diagnostic testing includes complete blood cell count, serum biochemistry analysis, and CSF evaluation.

Clinical pathology results are within normal limits in most cases, although results may reflect dehydration. Horses that are recumbent, or have difficulty standing, will have increased muscle enzyme

activity. In cases of wound botulism, the CBC may reflect signs of infection. CSF evaluation is normal in horses with botulism and helps to rule out many infectious and traumatic illnesses.

The clinical signs of botulism are fairly characteristic in the more advanced stages, but can be confusing early in the course of the disease. The absence of abnormal constitutional signs and clinical pathology results help to eliminate many infectious and toxic conditions. Principle diagnostic rule-outs for diffuse weakness and muscle fasciculations include white muscle disease, hyperkalemic period paralysis (HYPP), electrolyte abnormality (hypocalcemia and hypomagnesemia), and ionophore, white snake root, lead, and organophosphate toxicity. Rabies and yellow star thistle toxicity can result in dysphagia, but rabies will result in hyperexcitability and diffuse CNS inflammation. HYPP can be confused with botulism, but signs are episodic and is associated with an increase in potassium concentrations; neither being seen with botulism. Dysphagia can be caused by guttural pouch mycosis, and this can be confirmed or ruled out by endoscopic examination.

A diagnosis is further supported by (1) finding preformed toxin in the feed, GI contents, or wounds of an affected horse, (2) the demonstration of *C. botulism* spores in the GI contents or feed, or (3) the detection of an antibody response in a convalescent patient.[19] Definitive diagnosis requires confirmation of toxin in serum, plasma, GI contents, or wounds.

A mouse bioassay is the most sensitive test for the detection of botulinum toxin. Serum from a suspect horse is injected into ICR Swiss Webster mice, and they are observed for signs of botulism. Additional mice are pretreated with polyvalent antiserum and if protected, the presence of botulism toxin is confirmed. If necessary, further testing can be conducted using specific monovalent antiserum to determine specific toxin type. The mouse bioassay is rarely positive in clinical cases, however, because the horse is so susceptible to the toxin that it may demonstrate clinical signs when concentrations of toxin are so low that it does not produce clinical signs in the mice. Only a few cases have been reported in which the presence of circulating toxin was confirmed.

An enzyme-linked immunosorbent assay (ELISA) test has been developed for the assay of fluids for the presence of type C and type D botulinum toxin. This test is not considered as specific as the mouse bioassay, due to cross-reactivity with *C. novyi*. A polymerase chain reaction (PCR) test for the type B neurotoxin gene has also been developed and used in a research setting. Neither of these tests are currently commercially available, however.

Given the difficulty and rarity of detecting circulating toxin, botulism is most commonly supported by finding *C. botulinum* spores in feed or GI content. Spores are rarely reported in the feces of normal horses but are found in up to 70% of shaker foals. In one study, 3.2% of normal horses were found to have *C. botulinum* spores in feces.

Detection of antibody in serum of affected (but nonvaccinated) horses has been reported and may prove to be a useful means of confirming infection.

Electromyography has been described as a means to diagnose botulism in horses. Repetitive nerve stimulation produces a decremental response in evoked muscle. This is rarely described in the horse, and one author has reported it to be of minimal value in the diagnosis of botulism in horses.

Treatment

The fundamental principle of treating botulism in horses is the neutralization of circulating toxin. This is readily achieved by the administration of botulism antitoxin. If administered before adult horses become recumbent, the outcome is favorable in almost 70% of cases. If the antitoxin is not administered until after horses become recumbent, the chances for a successful outcome decrease significantly. The disease is highly fatal if horses are not treated with antitoxin, although mildly affected horses may survive. At the present time, polyvalent antitoxin can be obtained from the University of Pennsylvania, New Bolton Center (Dr Robert Whitlock). Adult horses should be treated with at least 500 ml of this product, and one treatment is usually adequate. In addition, a monovalent antitoxin (each of types B and C) is available (Veterinary Diagnostics, Inc., Templeton, California). In the author's experience, one treatment is usually adequate. Clinical signs may progress for a period of 12–24 h after antitoxin treatment, as antitoxin has no effect after the toxin has been internalized into the neuron. Early treatment is critical and will minimize the severity of the clinical signs.

Clearance of the organism may be necessary in cases of wound or toxicoinfectious botulism. In wound botulism, tissue debridement and disruption of the anaerobic environment are the most effective and may be aided by the use of antibiotics. Aminoglycosides, tetracyclines, and procaine penicillin are known to potentiate neuromuscular weakness and should be avoided. Potassium penicillin is preferred. Antibiotic treatment probably does not clear organism in the intestine, and their use in such cases may not be justified.

A variety of compounds have been proposed to counter the physiologic effects of botulinum toxin. Neostigmine and 4-aminopyridine will increase acetylcholine release in the NMJ and result in increased muscular strength in horses with botulism. The increased strength, however, is very temporary, and overall mortality is higher in horses treated with these compounds, as they exhaust the acetylcholine (ACH) that is present. They should not be used.

Nursing care of horses with botulism is critical to overall success. Affected horses should be maintained in a quiet environment such that they can conserve energy and do not have to compete with other animals. Horses frequently develop ileus, and withholding food is often necessary. Treatment with mineral oil to soften stool may aid passage, and manual evacuation of rectum and bladder are sometimes necessary. If horses are able to remain standing, they often develop dependent edema of the head, as it remains in a dependent position. The head can be tied up, and nasotracheal tubes can be passed to maintain a patent airway and block muzzle swelling. Hydration status can be maintained with oral fluids, or, if ileus is present, using intravenous fluids. Horses may aspirate food material and can develop aspiration pneumonia; hence, they may need to be withheld from eating. Nutritional support is necessary and can be achieved by feeding a slurry through a feeding tube, or more effectively using intravenous nutrition. Antibiotic treatment is necessary in horses with aspiration pneumonia. Ocular lubricants are useful as some horses develop dry-eye.

Horses with botulism should not be maintained in a sling, as this tends to exhaust them and leads to increased mortality. Severely affected animals develop respiratory distress due to hypoventilation, which is the ultimate cause of death. Use of a sling compresses the chest and further compromises respiration. Mechanical ventilation is required in severe cases and is highly rewarding in foal cases, but is probably not possible in horses that weigh more than 400 pounds. Horses that are recumbent usually remain so for about 7–10 days, so treatment of such animals should not begin unless the owner is committed to a lengthy hospitalization. Muscular recovery takes up to 10 days which is the time required for regeneration of docking proteins in the NMJ—return to full strength may take up to 1 month.[19] Improvement in muscle strength may be noted prior to this, but will not be complete and will be dependent upon the initial degree of weakness present. The more severe the weakness, the longer recovery takes.

The outcome is dependent upon the amount of toxin present. As it is not generally possible to know this at the time of initial presentation, prognosis is difficult. Success of treatment of adults is often determined by the complications of recumbency, with pneumonia and decubital ulceration being the most common complications.

Prophylaxis

In North America, a vaccine against type B botulism is currently available. An initial vaccination is followed by a booster in 3 weeks, with annual revaccination recommended. The vaccine appears to be highly effective, but infection with other serotypes is possible. Horses that reside in an endemic area should be vaccinated, as well as horses which are fed round bale hay or silage. Pregnant mares in endemic areas should be vaccinated and boostered 4–6 weeks before anticipated foaling. Foals from unvaccinated mares can be transiently and passively protected using the antitoxin, or vaccinated with the toxoid, although it is not labeled for foals.

REFERENCES

1. Coleman ES. 1998. Clostridial neurotoxins: tetanus and botulism. *Compend Contin Educ Pract Vet* 20:1089–96.
2. Bleck T. 1986. Pharmacology of tetanus. *Clin Neuropharmacol* 9:103–20.
3. Montecucco C, Shiavo G. 1994. Mechanism of action of tetanus and botulinum neurotoxins. *Mol Microbiol* 13:1–8.
4. Timoney JF, Gillespie JH, Scott FW, *et al*. 1988. The genus *Clostridium*. In *Hagan and Bruner's*

Microbiology and Infectious Diseases of Domestic Animals, edited by Timoney JF, Gillespie JH, Scott FW, Barlough JE, 214–22. Ithaca: comstock Publishing Associates.
5. Hahn CN, Mayhew IG, MacKay RJ. 1999. Diseases of the brainstem and cranial nerves. In *Equine Medicine and Surgery,* edited by Colahan PT, Merritt AM, Moore JN, Mayhew IG, 931–41. St. Louis: Mosby, Inc.
6. Green SL, Little CB, Baird JD, *et al*. 1994. Tetanus in the horse: a review of 20 cases (1970–1990). *J Vet Intern Med* 8:128–32.
7. Goonetilleke A, Harris JB. 2004. Clostridial neurotoxins. *J Neurol Neurosurg Psychiatry* 74(Suppl. 3):35–9.
8. Wright DK, Lalloo UG, Nayiager S. 1989. Autonomic nervous system dysfunction in severe tetanus: current perspectives. *Crit Care Med* 17: 371–5.
9. Muylle E, Oyaert W, Ooms L, *et al*. 1975. Treatment of tetanus in the horse by injections of tetanus antitoxin into the subarachnoid space. *J Am Vet Med Assoc* 167:47–8.
10. Odusote KA, George BO, Femi-Pearse D. 1976. Favorable prognosis of prolonged coma associated with large doses of diazepam in severe tetanus. *Trop Geogr Med* 28:194–8.
11. Weinstein L. 1973. Current concepts: tetanus. *N Engl J Med* 289:1293–6.
12. Smithcors JF. 1956. The treatment of tetanus with curare–A little known chapter in veterinary history. *J Am Vet Med Assoc* 129:303–5.
13. Jansen BC, Knoetze PC. 1979. The immune response of horses to tetanus toxoid. *Onderstepoort J Vet Res* 46:211–6.
14. MacKay RJ, Berkhoff GA. 1982. Type C toxicoinfectious botulism in a foal. *J Am Vet Med Assoc* 180:163–4.
15. Semrad S, Peek S. 2002. Equine botulism. *Compend Contin Educ Pract Vet* 24:169–72.
16. Heath SE, Bell RJ, Harland RJ. 1988. Botulinum type C intoxication in a mare. *Can Vet J* 29:530–1.
17. Kinde H, Betty RL, Ardans A. 1991. *Clostridium botulinum* type-C intoxication associated with consumption of processed hay cubes in horses. *J Am Vet Med Assoc* 199:742–6.
18. Hutchins R. 1994. Preliminary report on an outbreak of botulism. *Aust Equine Vet* 12:54–5.
19. Whitlock RH, Buckley C. 1997. Botulism. *Vet Clin North Am Equine Pract* 13:107–28.
20. Switzer JW, Jensen M, Reimann HP. 1984. An outbreak of suspected Type D botulism in horses in California. *Calif Vet* 7:14–7.
21. Hunter JM, Rohrbach BW, Andrews F, *et al*. 2002. Round bale grass hay: a risk factor for botulism in horses. *Compend Contin Educ Pract Vet* 24:169–72.
22. Broughton J, Parsons L. 1985. Botulism in horses fed big bale silage. *Vet Rec* 117:674.
23. Wichtel JJ, Whitlock RH. 1991. Botulism associated with feeding alfalfa hay to horses. *J Am Vet Med Assoc* 199:471–2.
24. Ricketts SW, Greet TCR, Glyn PJ, *et al*. 1984. Thirteen cases of botulism in horses fed big bale silage. *Equine Vet J* 16:515–8.
25. Divers TJ, Bartholomew RC, Messick JB, *et al*. 1986. *Clostridium botulinum* type B toxicosis in a herd of cattle and a group of mules. *J Am Vet Med Assoc* 188:382–6.
26. Goehring LS, van Maanen C, van Oldruitenborgh-Oosterbaan S. 2005. Neurologic syndromes among horses in The Netherlands. A 5 year retrospective survey (1999–2004). *Vet Q* 27:11–20.
27. Haagsma J, Haesebrouck F, Devriese L, *et al*. 1990. An outbreak of botulism type B in horses. *Vet Rec* 127:206.
28. Bernard W, Divers TJ, Whitlock RH, *et al*. 1987. Botulism as a sequel to open castration in a horse. *J Am Vet Med Assoc* 191:73–4.
29. Mitten LA, Hinchcliff KW, Holcombe SJ, *et al*. 1994. Mechanical ventilation and management of botulism secondary to an injection abscess in an adult horse. *Equine Vet J* 26:420–3.
30. Swerczek TW. 1980. Experimentally induced toxicoinfectious botulism in horses and foals. *Am J Vet Res* 41:348–50.
31. Swerczek TW. 1980. Toxicoinfectious botulism in foals and adult horses. *J Am Vet Med Assoc* 176: 217–20.
32. Whitlock RH. 1995. Botulism type C experimental and field cases in the horse. *Proc 13th Annual Meet ACVIM* 13:720–3.

18
Miscellaneous Infections of the Central Nervous System

Martin Furr

CRYPTOCOCCAL MENINGITIS

Cryptococcosis is a fungal disease of humans and animals. The encapsulated yeast-like fungus is an opportunistic pathogen of debilitated or immunologically compromised individuals. *Cryptococcus neoformans*[1–5] is most commonly implicated, although infections with *Cryptococcus albidus* and *Cryptococcus laurentii* have been seen.[6]

Cryptococcal infections in the horse usually cause rhinitis,[7,8] sinusitis,[5] or pneumonia[6] and occasionally meningitis and encephalitis.[1–4,9,10] Several reports are noted from Australia, where an association between the Eucalyptus plant (*Eucalyptus camaldulensis*) and the infection has been suggested.[6] In addition, an association between animals that have contact with soil contaminated with pigeon droppings is suspected.[4]

Clinical Signs

Clinical signs can vary depending upon the location of the infection within the central nervous system (CNS); however, diffuse signs of encephalitis seem to predominate. Asymmetric signs were reported in one horse.[10] Depression and anorexia are often noted, as are gait stiffness, hyperesthesia, and ataxia. Sudden death was also reported in one case.[3] Variable types and degrees of cranial nerve deficit may also be seen, including blindness, nystagmus, and fixed and dilated pupils.[4] Hind limb paralysis, rectal and bladder paralysis, penile paralysis and gluteal muscle wasting have all been reported.[2,10] In many cases, the cardinal signs are normal, although mild fever and anorexia may be seen. Blindness was noted in a horse with post-orbital mass, leading to pressure necrosis of the optic nerve as the granulomatous mass bulged into the cranial cavity displacing the left cerebral hemisphere.[5]

Diagnosis

The antemortem diagnosis of CNS cryptococcosis is challenging, as the clinical signs are non-specific. Bacterial, viral, and parasitic infections of the nervous system should be considered in the differential diagnosis. Peripheral white blood cell counts are variable in reported cases, and serum biochemistry results highlight only non-specific changes resulting from dehydration and recumbency. The diagnosis is primarily dependant upon analysis of cerebrospinal fluid (CSF). CSF results are very poorly reported from previous studies;[9] however, discolored, turbid fluid with an increased total protein and white blood cell count is expected. A mixed inflammatory reaction, with roughly equal numbers of neutrophils and macrophages was observed in one case.[9] Budding yeasts surrounded by a thick, non-staining capsule may be seen, but non-encapsulated form may also be observed in the CSF. The presence of the capsule can be demonstrated by performing an India ink counterstain.

Postmortem diagnosis reveals the surface of the brain/spinal cord to be covered with small nodules. Meninges may be thick and discolored yellow, with a gelatinous exudate on the surface.[3] Wet mount of a surface impression may reveal thick-walled capsular organisms. Histologic analysis finds a granulomatous inflammatory reaction, with few deep organisms surrounded by minimal local inflammation.[4]

Treatment

Treatment of horses with cryptococcal meningitis is not well reported, and recommendation for treatment

protocols must be extrapolated from human medicine. In humans, a two-phase treatment protocol is advised by some authors.[11] In a group of non-HIV infected humans with cerebral cryptococcosis, best results were obtained using a treatment protocol of amphotericin B intravenously and intrathecally (phase 1), followed by oral fluconazole (phase 2). During phase 1, intrathecal treatment was administered 2–3 times per week until the CSF culture was negative. Amphotericin B should be diluted (1 mg/mL) in sterile water for injection and mixed with autogenous CSF. Due to the irritant properties of amphotericin B, corticosteroids can be given either intrathecally or systemically. Phase 2 of the combination protocol employs long-term oral fluconazole or itraconazole until the CSF is culture negative 3 times, one week apart. Treatment duration in a human study ranged up to 16 months in one case, with an average of about 7 months.[11] Overall success using the two-phase approach was 97.5%, while single treatments with fluconazole, itraconazole or amphotericin B had a much lower success rate, and more recurrences.[11]

Obviously, treatment of cryptococcal meningitis is challenging, and a poor prognosis must be given for equine cases due to the expense and complexities of long-term management of a neurologic horse. Appropriate supportive care as well as long-term anti-inflammatory and anti-fungal medications are required. There is only one report of treatment of cryptococcal meningitis in a horse; however, it responded transiently to a protocol using amphotericin B. Amphotericin B (100 mg, then increased to 150 mg) was diluted in 4000 mL of 5% dextrose and administered IV over 4 h. This was given every other day for a total of 12 treatments.[9] Intrathecal treatment with 50 mg amphotericin B was also attempted. A deteriorating condition and seizures the following day prompted euthanasia, and the authors suggested that a lower dose of intrathecal amphotericin B (15 mg) would have been advisable.[9] The experience of this case, and that of the treatment of humans would suggest that a two-phase protocol of intravenous and intrathecal amphotericin B, followed by oral fluconazole would be advisable.

AMEBIC MENINGOENCEPHALITIS

A single case of equine meningoencephalitis caused by the amebic organism *Balamuthia mandrillaris* (leptomyxid ameba) has been reported.[12] A 20-year-old horse showed acute signs of salivation and stumbling, progressing to recumbency followed by euthanasia over a 2-day period. No aspects of clinical pathology or CSF analysis were reported. Post mortem examination found numerous small (3 mm) irregularly shaped pale tan lesions in the midbrain and cervical spinal cord. Upon microscopic examination, these were associated with extensive necrosis with perivascular inflammatory cell infiltrates. Both trophozoites and cyst forms were observed. Immunohistochemical staining confirmed them to be *B. mandrillaris.* Other pathogenic ameba are recognized as free-living organisms in ponds, lakes, soil and upon vegetables; however, *B. mandrillaris* has been isolated only from human and animal tissues.[13] It is believed that the organism gains entry via the ethmoturbinates, respiratory tract, or skin wounds, or ascends via the optic nerve.

Treatment is symptomatic (anti-inflammatory drugs and supportive) along with anti-amebic compounds. Fluconazole, amphotericin B, and miconazole demonstrate some activity against the parasite, but there is a high mortality in human patients,[14] and a grave prognosis must be given if diagnosed antemortem.

MYCOTIC ENCEPHALITIS

Fungal infections other than cryptococcosis have also been (rarely) incriminated in equine neurologic disease.[15–17] Reported cases appear to have occurred secondary to guttural pouch mycosis. Clinical signs reflect brainstem and cerebral disease with dysphagia, head shaking, ataxia, blindness and seizures occurring variably. In one case, CSF taken from the atlanto-occipital (AO) space found a CSF pleocytosis (79 cells/mm^3), predominately mononuclear cells but 19% neutrophils.[18] A strong positive Pandy test was present and fungal elements were not seen.

Histopathologic examination finds numerous areas of inflammation and necrosis, characterized by infiltration with neutrophils and mononuclear cells, thrombosis of vessels, and fungal elements. The fungus may obtain access to the brain by direct migration up a cranial nerve; however, hematogenous dissemination was considered most likely in one case, due to the degree of thrombosis and lack of obvious cranial nerve involvement.[15]

Prognosis for such cases is very poor, but if treatment is attempted, the use of antifungal medications

(as discussed above) and anti-inflammatory drugs would be indicated.

NEUROBORRELIOSIS

Infection with *Borrelia burgdorferi* is widely distributed in the Northern Hemisphere[19] and results in a syndrome of dermatitis, myalgia, arthritis, and aseptic meningitis in humans.[20] Similar clinical signs have been ascribed to the horse; however, there is very little evidence confirming CNS disease in these cases. A compelling diagnosis for neuroborreliosis was made in one horse demonstrating clinical signs of abnormal mentation, head tilt, flaccid paralysis of the tail, and dysphagia.[21] The diagnosis in this case was based upon a high *B. burdorferi* titer and the presence of spirochetes in the brain on post-mortem examination.[21] Methods for clinical diagnosis of equine neuroborreliosis are not described, but elimination of other more likely pathogens, presence of a high titer and residence in an endemic area would be supportive. Treatment recommended for non-nervous system Lymes disease is a prolonged antibiotic course using tetracycline, doxycycline or ceftiofur. The value of these treatments in CNS infections is unproven.

REFERENCES

1. Cho DY, Pace LW, Beadle RE. 1986. Cerebral cryptococcosis in a horse. *Vet Pathol* 23:207–9.
2. Barton MD, Knight I. 1972. Cryptococcal meningitis of a horse. *Aust Vet J* 48:534.
3. Irwin CFP, Rac R. 1957. Cryptococcus infection in a horse. *Aust Equine Vet* 33:97–8.
4. Welsh RD, Stair EL. 1995. Cryptococcal meningitis in a horse. *J Equine Vet Sci* 15:80–2.
5. Scott EA, Duncan JR, McCormack JE. 1974. Cryptococcosis involving the postorbital area and frontal sinus in a horse. *J Amer Vet Med Assoc* 165:626–7.
6. Riley CB, Bolton JR, Mills JN, *et al.* 1992. Cryptococcosis in seven horses. *Aust Vet J* 69:135–9.
7. Corrier DE, Wilson SR, Scrutchfield WL. 1984. Equine cryptococcal rhinitis. *Comp Cont Educ Pract Vet* 6:S556–8.
8. Phillips MT. 1969. Equine cryptococcus. *Southwestern Vet* 22:147–8.
9. Steckel RR, Adams SB, Long GG, *et al.* 1982. Antemortem diagnosis and treatment of cryptococcal meningitis in a horse. *J Amer Vet Med Assoc* 180:1085–9.
10. Barclay WP, de Lahunta A. 1979. Cryptococcal Meningitis in a Horse. *J Amer Med Assoc* 174:1236–8.
11. Yao Z, Liao W, Chen R. 2005. Management of cryptoccosis in non-HIV-related patients. *Med Mycol* 43:245–51.
12. Kinde J, Visvesvara GS, Barr BC, *et al.* 1998. Amebic meningoencephalitis caused by *Balamuthia mandrillaris* (leptomyxid ameba) in a horse. *J Vet Diagn Invest* 10:378–81.
13. Denney CF, Iragi VJ, Uber-Zak LD, *et al.* 1997. Amebic meningoencephalitis caused by *Balamuthia mandrillaris*: case report and review. *Clin Infect Dis* 25:1354–8.
14. Intalapaporn P, Suankratay C, Shuangshoti S, *et al.* 2004. *Balamuthia mandrillaris* meningoencephalitis: the first case in southeast Asia. *Am J Trop Med Hyg* 70:666–9.
15. McLaughlin BG, O'Brien JL. 1986. Guttural pouch mycosis and mycotic encephalitis in a horse. *Can Vet J* 27:109–11.
16. Wagner PC, Miller RA, Gallina AM, *et al.* 1978. Mycotic encephalitis associated with a guttural pouch mycosis. *J Equine Med Surg* 2:355–9.
17. Hatziolos BC, Sass B, Albert TF, *et al.* 1975. Blindness in a horse probably caused by gutturomycosis. *Zentralb Veterinaermed* 22:362–71.
18. Wagner PC, Miller RA, Gallina AM, *et al.* 1978. Mycotic encephalitis associated with guttural pouch mycosis. *J Equine Med Surg* 2:355–9.
19. Madigan JE. 1993. Lyme disease (Lyme Borreliosis) in horses. *Vet Clin North Am Equine Pract* 9:429–34.
20. Shaprio ED, Gerber MA. 2000. Lyme disease. *Clin Infect Dis* 31:533–42.
21. Burgess EC, Mattison M. 1987. Encephalitis associated with *Borrelia burgdorferi* infection in a horse. *J Amer Vet Med Assoc* 191:1457–8.

19
Neurodegenerative Disorders

Robert MacKay

EQUINE DEGENERATIVE MYELOENCEPHALOPATHY

History and Epidemiology

Equine degenerative myeloencephalopathy (EDM) was first reported by Mayhew[1,2] in 1976 as an acute to insidious onset symmetric ataxia and weakness of the trunk and limbs in 5 horses of various breeds as well as a captive zebra. The signs began as early as birth and as late as 12 months of age. Affected horses had diffuse degenerative changes in the spinal cord and brainstem with involvement of the cuneate, gracilis, and lateral spinal cord nuclei. Since the original description, EDM has been reported in the United States in a donkey[3] and in horses of the Thoroughbred,[4,5] Quarter Horse,[4,5] Standardbred,[2,4,5] Arabian,[5] Appaloosa,[6] Paso Fino[7] (MacKay, unpublished results, 1999), Morgan,[5] Hanoverian,[8] Tennessee Walking Horse,[8,9] Welsh Pony,[3] Trakehner,[5] Norwegian Fjord,[9] and Andalusian (MacKay, unpublished results, 2001) breeds and in Haflingers[10] and Quarter Horses[11] in Europe. Reported cases in the United States have been from the northeastern, southeastern, midwestern, and northwestern regions, but the condition likely occurs throughout North America. The clinical and histologic changes of EDM are similar to those described by Beech[12,13] for neuroaxonal dystrophy of Morgan horses. In comparison with the original description of EDM as a degenerative process involving myelin and axons of neurons in the lateral cuneate and thoracic nuclei, the syndrome described in the young Morgan horses was limited to the lateral cuneate nuclei.[14] Other syndromes resembling EDM have been reported as spinal ataxia in captive Grant zebras[15] and myelopathy in captive Przewalskii horses.[16]

Clinical signs usually begin within the first year of life; however, one horse was reported to have developed signs of EDM at 12 years of age.[5] In a series of 43 cases,[5] 19 began at 1–7 months old, 15 at 9–14 months, 6 at 16–28 months, and 3 between 5 and 12 years of age.

A hereditary basis for the condition in some horses has been strongly suggested by the results of limited breeding studies. A clinically normal Appaloosa mare in Oregon produced 4 foals, 3 of which were affected.[6] One of these foals, a colt, subsequently sired 7 foals of which 4 were diagnosed with EDM. Of the 24 Morgan foals produced in a breeding study when one of the parents was clinically affected with neuroaxonal dystrophy, 18 were confirmed or suspected to have the condition by one year of age.[13] The mode of inheritance in the latter study was suspected to be polygenic or dominant with variable expression.[13] A familial basis also has been suspected because of the clustering of cases among the progeny of particular Standardbreds,[7] Paso Finos,[7] Norwegian Fjord horses,[9] Arabians,[4] Welsh ponies,[9] and Haflingers.[10] In a retrospective study of risk factors for EDM, it was found that a foal was 25 times more likely to develop EDM if its dam had any other progeny with the disease.[5]

Overcrowding, lack of access to fresh green forage, pelleted feed, and poor quality hay were thought to be risk factors on 2 affected premises.[7] In a retrospective questionnaire-based study of 56 cases admitted to Cornell University, risk factors identified were exposure to insecticides/repellents, exposure to wood preservatives such as creosote,

and time spent on dirt lots.[17] Time spent on green pasture was a protective factor. By contrast, in a cluster of cases in Oregon, a common nutritional or environmental factor could not be identified, and all affected horses had access to pasture.[6]

With the exception of one study, there has been a consistent association reported between EDM and marginal or low serum/plasma α-tocopherol concentration. Published normal ranges for α-tocopherol vary with age, location, season, diet, and use; however, a commonly accepted scheme classifies results >2.0 μg/mL as normal, 1.5–2.0 μg/mL as marginal, and <1.5 μg/ml as deficient.[7,18] Affected horses in Oregon had plasma α-tocopherol concentration of 1.43 ± 0.90 μg/mL compared with 2.67 ± 1.38 μg/mL for normal horses in the same region.[6] For clusters of EDM cases in the United States and Italy, serum α-tocopherol was 0.62 ± 0.13 μg/mL and 1.54 ± 0.60 μg/mL, respectively.[7,11] Two full-sibling Haflinger fillies in Germany that had EDM had serum α-tocopherol of 0.22 and 0.23 μg/mL.[10] Set against these findings of low serum vitamin E are the results of Dill *et al*.[17] at Cornell University that median serum vitamin E concentration in 39 horses with EDM was not different than that of age-matched control patients (e.g., for animals <1 year, median values in EDM cases and controls were 3.10 and 2.50 μg/mL, respectively).[17]

During the approximately 15 years after it was first recognized, EDM was one of the most prevalent causes of spinal cord disease in horses presented to teaching hospitals in the United States. EDM was the diagnosis in 22/95 (23%) horses presented to Cornell for spinal cord disease between 1975 and 1977.[4] From 1977 to 1987 at Cornell, 383 horses were diagnosed with EDM compared to 121 with cervical vertebral stenotic myelopathy and 91 with equine protozoal myeloencephalopathy (EPM).[17] Approximately 20% of the ataxic horses presented to Oregon State University up until 1992 had a histologic diagnosis of EDM.[9] Although no statistics on prevalence have been published in recent years, it is apparent that the prevalence of EDM has declined in the United States since about 1990.

Cause and Pathogenesis

EDM most closely resembles vitamin E deficiency of humans and other animals. Clinical signs that may include ataxia and hyporeflexia develop in humans with vitamin E deficiency secondary to chronic intestinal malabsorption, cholestasis, or liver disease[19–21] and in rats on vitamin E-deficient diets.[22] A familial tendency to low vitamin E has been reported in pigs,[23] and in humans, familial isolated vitamin E deficiency, an autosomal recessive spinocerebellar disorder, has been associated with mutations in the gene for α-tocopherol transfer protein.[24] Interestingly, foals in an Appaloosa family with hereditary EDM had significantly lower plasma vitamin E than did age-matched normal pasture mates.[25] This effect was continuous from 6 weeks to 10 months of age. Results of oral vitamin E tolerance tests (OVETT) in EDM horses were comparable to those for normal horses, suggesting that the relatively low plasma vitamin E in EDM horses was not caused by reduced intestinal absorption.[25] In humans with familial isolated vitamin E deficiency, the absorption phase of OVETT is normal, but the decline is more rapid than is found in controls.[26] This finding is caused by a defect in the hepatic transfer of vitamin E from chylomicrons to lipoprotein carriers. It is reasonable to speculate that a comparable defect in vitamin E metabolism, involving factors such as lipoprotein carriers, hepatic transfer proteins, or vitamin E receptor sites, may be involved in the pathogenesis of EDM.[25]

It is not yet clear whether all EDM cases share a common pathogenesis. Horses with EDM admitted to Cornell had serum vitamin E concentration comparable with age-matched controls and within normal published ranges, indicating that vitamin E deficiency may not be a necessary feature of EDM;[17] however, it has been suggested by Blythe *et al*.[25] that normal results at the time of referral may not have reflected the vitamin E status of these horses at the time of clinical onset.

Clinical Signs

EDM is an insidious to acute onset symmetric ataxia and paresis of the trunk and limbs. (Figure 19.1) The onset of clinical signs typically occurs between 1 and 12 months of age but has been reported in neonates and in mature horses.[2,4–7,9,10,17] There is notable hypometria (spasticity) in affected limbs. Signs typically are considerably more severe in the pelvic limbs, and the thoracic limbs may be clinically normal. On the basis of a clinical severity score of 0+ to 4+ for thoracic/pelvic limbs, Mayhew *et al*.[7] recorded examination scores of 0+/2+, 1+/2+, 1+/3+, 1+/4+, and 2+/4+ in horses with



Figure 19.1. Interference between thoracic limbs (left) and collapse of and pivoting around the pelvic limbs in a 4-month-old Andalusian filly. This filly had shown clinical signs of limb ataxia and weakness since approximately 1 week of age. A full sibling born a year earlier also developed signs of EDM shortly after birth.



Figure 19.2. Two-beat "pacing" gait at walking speed in a yearling American Paso Fino filly. Limb ataxia was first noticed at approximately 1 month of age. The sire of this filly produced at least 15 other progeny that developed EDM.

EDM. As is seen occasionally in horses with any spinal cord disease, some horses with EDM adopt a 2-beat lateral ("pacing") gait at walking speed (Figure 19.2).

Long spinal reflexes such as the cervicofacial, laryngeal adductor (slap), and cutaneous trunci are often reduced or absent, especially in long-standing cases.[6,7] Neurogenic muscle atrophy is not seen in horses with EDM. Signs progress for days to months before stabilizing. Only rarely does the condition progress to recumbency.[7]

Laboratory Findings and Ancillary Testing

There is no antemortem diagnostic test for EDM. Plasma/serum vitamin E concentrations of EDM horses and pasture mates are often marginal or low. Because vitamin E concentrations within individual horses vary considerably over time, it was suggested

that 3 blood samples be taken over the course of 24 h.[25] Plasma creatine kinase (CK) and aspartate aminotransferase (AST) activities may be slightly to moderately high because of increased recumbency.[6]

Oral vitamin E absorption has been described for the horse.[27] The recommended technique is administration of 90 IU of dl-α-tocopherol/kg mixed with 60 mL corn oil in 1 L of grain to horses from which food has been withheld for 12 h. Vitamin E measurements are made at 3, 6, 9, 12, and 24 h after vitamin E administration. Results for one group of EDM horses were comparable to those of controls.[25]

Diagnosis

Diagnosis antemortem is presumptive only and is made primarily by suggestive signalment and clinical signs with the exclusion of competing diagnoses. EDM should be suspected in horses with symmetric limb ataxia and weakness that began within the first year of its life and for which results of standard neurologic workups (cervical vertebral radiographs, cerebrospinal fluid (CSF) analysis, immunoassay for *Sarcocystis neurona* antibody) have not implicated another diagnosis. Low serum/plasma vitamin E concentration (<1.5 g/mL) is supportive of the diagnosis.

Necropsy Findings

There are no abnormal gross necropsy findings. Histologic changes develop in the spinal cord and brain stem.[4,6,7,10] Active or chronic neuronal fiber degeneration occurs symmetrically throughout the spinal cord but is most severe in the ventral and medial parts of the ventral funiculi and the spinocerebellar tracts (lateral funiculi). In the sensory relay nuclei in the spinal cord and brainstem, there is spheroid formation with vacuolation, loss of somata, astrogliosis, and lipofuscin pigment accumulation. Spheroids are especially prominent in the thoracic and lateral cuneate nuclei (EDM) or lateral cuneate nuclei only (neuroaxonal dystrophy of Morgans).

Treatment and Prevention

It is unlikely that EDM can be cured even if treated early. Vitamin E treatment is rational, however, and neurologic scores of EDM horses improved when fed 6000 IU/day of d,l-α-tocopherol.[28] Continuous but ultimately incomplete improvement was seen throughout 12 months of therapy. Treatment was more successful when treatment was begun immediately after the onset of signs. Blythe and Craig[28] have suggested that daily treatment should be continued until 3 years of age.

Consistent with the notion that EDM is associated with some interaction between metabolic defect and vitamin E deficiency, vitamin E supplementation appears to be effective prophylaxis and is highly recommended in circumstances in which there is familial predisposition, processed feed, lack of access to pasture, and exposure to insecticides or wood preservatives. In one study, the incidence of EDM was reduced from 36% over 3 years to 9% in the following year by supplementation of foals with 1500 IU vitamin E daily. Obviously, sensible genetic, nutritional, and other management practices alone could greatly reduce or eliminate the risk of EDM.

EQUINE MOTOR NEURON DISEASE

History and Epidemiology

Between 1985 and 1997, more than 200 cases of equine motor neuron disease (EMND) were identified and reported.[29] Although many states in the United States had at least one case during that period, there was a clear geographic gradient of incidence for EMND that was highest in the New England states and dropped off sharply to the west and south.[30] Cases were reported in Great Britain,[31,32] Canada,[33] Ireland,[34] Switzerland,[35] Belgium,[36] Japan,[37] Brazil,[38] and the Netherlands.[39] During the decade up to about 1997, more cases of EMND were recognized each year, perhaps because of increasing awareness of the disease among veterinarians and horse owners.[29] Since that time, the incidence of EMND, at least as reflected by admissions to Cornell University,[40] appears to have declined as owners have adjusted husbandry practices to minimize exposure to known risk factors.

The disease usually occurs sporadically, with only one case on a given premise at any time; however, one or more additional cases have occurred on the same premise within 2 years of the original diagnosis.[40] An unusual cluster of more than 80 cases was seen among horses in a city police cavalry in Brazil during the 1990s.[40]

The reported age range of affected horses is 2 to 23 years in the United States[29] and 2 to 27 years

in Europe.[41] There is brief reference to a case of EMND in a 9-month foal[42]; however, this claim is not repeated in subsequent reviews by these same authors. In logistic models of risk factors for EMND in the northeastern United States, risk increased with age until 15[30] or 16[42] years and then declined.

The first case-control study of EMND examined signalment data from 32 cases identified in the United States between 1985 and 1991.[42] In the final multivariate logistic regression model, only age and Quarter Horse breed were significant risk factors for EMND. Analysis of a clinical series of 28 cases presented to Cornell between 1990 and 1993[43] showed Quarter Horses to be significantly over represented. Twenty-six of the horses had been confined to a stall or dirt paddock for at least a year before onset of EMND, and most were fed high amounts of concentrates but poor quality hay. Of particular significance, plasma vitamin E concentrations of cases were significantly lower than those of on-farm controls. A case-control study of 87 cases that were presented to Cornell between 1990 and 1995[30] examined 64 potential, intrinsic, medical history, management, and nutritional factors. Of these, age, Quarter Horse breed, residency on the same premise for 2–7 years (compared with <2 years), lack of rabies vaccination during the previous 2 years, and history of wood-chewing or coprophagia were significant risk factors for EMND. Lack of access to pasture, use of pelleted feed (alone or with sweet feed), and frequent supplementation with vitamin/mineral supplements lacking vitamin E/selenium were significant nutritional risk factors in the final model. Fifty-three of these horses were included in a case-control study of plasma vitamin E concentration as a risk factor for EMND.[44] After controlling for other risk factors, a significant negative association was demonstrated between vitamin E concentration and EMND risk. Of a series of 32 cases identified in Europe between 1996 and 2004,[41] 13 had part- or full-time exposure to pasture; however, all affected horses had low plasma vitamin E concentrations, suggesting that bioavailability of ingested vitamin E was low in these horses. A horse in Finland developed EMND despite supplementation with 300 mg α-tocopherol daily for the previous 10 years.[45] In that case, daily supplementation with excessive amounts of iron (Fe) was suggested as a possible cause. In the United States, horses with EMND that had normal access to pasture had enteric or hepatic disease, presumably resulting in malabsorption of vitamin E.[29,43]

Pathogenesis

EMND is a spontaneous, progressive, sporadic, and even solitary condition that does not have the epidemiologic characteristics of an infection, toxicity, or simple inherited disorder. Attempts to identify an etiologic infectious agent reportedly have failed, as have transmission experiments using plasma and sera from horses with progressive EMND.[30]

It was recognized early on that the histopathologic findings of degeneration and loss of motor neurons in the brainstem and spinal cord of horses with EMND were similar to those found in human beings with sporadic amyotrophic lateral sclerosis (ALS).[46] In fact, the distribution of central nervous system (CNS) lesions in EMND closely resembles those of an ALS variant, progressive spinal muscular atrophy.[42] Although sporadic ALS is likely multifactorial, it is widely believed that oxidative stress is involved in the final common pathways of neuronal injury.[47] In support of this notion, a form of familial ALS is associated with a mutation in the gene for copper (Cu)/zinc (Zn) superoxide dismutase (also known as SOD1).[47]

Consistent with the notion that systemic oxidant stress is involved in the pathogenesis of EMND, atrophy in affected horses is focused on type 1 myofibers. Type 1 fibers are more oxidatively active than type II fibers.[48] Also, deposits of ceroid lipofuscin are found in the retinal pigmented epithelium and in the endothelium of spinal cord capillaries.[29] Massive accumulations of lipofuscin were found in the pigmented epithelium of rats lacking various antioxidants including vitamin E[49]; such deposits are thought to be the end products of peroxidation of membrane polyunsaturated fatty acids.[50]

Low blood and spinal cord vitamin E concentrations have consistently been found in horses with EMND in the United States and an epidemiologic study linked low serum vitamin E to EMND risk (see Epidemiology section). The typical history for EMND cases also includes lack of access to green forage, so vitamin E deficiency is thought to be involved in the pathogenesis of the disease. Because most horses on vitamin E-deficient diets do not develop EMND, other factors must act to increase the susceptibility of an individual horse to the

effects of low vitamin E intake. Accordingly, it can be hypothesized that dietary vitamin E deficiency only becomes significant in one or more of the following settings:

1. *Absorption, metabolism, or retention of ingested vitamin E is impaired.* Such a scenario has been suspected in the approximately 5% of horses with EMND that have infiltrative/inflammatory bowel disease or advanced liver cirrhosis.[29]
2. *Other dietary antioxidants or endogenous antioxidant systems are deficient or inadequate.* Support for this hypothesis is lacking. Plasma vitamin A, β-carotene, and ascorbic acid concentrations have usually been normal in horses with EMND.[51] Erythrocyte SOD1 activity is reduced in many horses with EMND;[52] however, low SOD1 activity is not associated with mutations in the SOD1 gene.
3. *Dietary pro-oxidant factors are excessive.* In this regard, there is particular interest in the potential roles of Fe and Cu. Divers[29] has noted that the initial identification of EMND cases occurred about the same time (late 1980s) as the amount of Cu in equine concentrates was substantially increased. Salts of both transition metals can participate in the Fenton and Haber-Weiss reactions and generate potentially injurious oxygen radicals. High concentrations of Fe were found in the liver of many horses with EMND (mean 540 ppm vs. 200–500 ppm for normal horses).[40] Spinal cord concentration of Cu was significantly higher in EMND compared to age-matched control horses (mean of 5.4 vs. 4.6 μg/g, respectively).[53] Interestingly, black tartar has been noted on the incisors of some affected horses, and analysis of the tartar revealed high concentrations of Cu, Fe, and phosphorus (P).[29] A recently reported case of EMND in a Standardbred stallion with normal serum vitamin E concentration was attributed by the authors to daily consumption for 10 years of 650 mg Fe (as Fe fumarate).[45] In one European case series, a comparatively high proportion of cases (13/32) had full- or part-time access to pasture,[41] suggesting that factors other than vitamin E intake were operative in the development of the disease.

On the basis of hypotheses connecting vitamin E, Fe, and Cu to EMND, 8 experimental horses were kept on a dirt lot and fed grass hay stored >1 year and concentrate that was low in vitamin E and high in Cu and Fe.[54] Four horses developed obvious clinical signs and pathologic findings of EMND after 21–28 months on the diet. Horses on a control diet remained healthy. Although these results support the concept of a role for oxidative stress in EMND, the individual contributions of vitamin E, Cu and Fe could not be discerned from this experiment. In a parallel experiment, the complete results of which are not yet published, 5/10 horses developed EMND after at least 18 months under conditions that were as above except for normal Cu and Fe content in the concentrate.[40] Taken together, the results of these experiments and clinical case series confirm that a diet low in vitamin E is a very strong risk factor for EMND. Left unresolved is the question whether or not vitamin E intake is the *only* responsible nutritional or management factor influencing the development of EMND in these experimental horses and in other affected horses around the world.

Clinical Signs

The clinical signs of EMND reflect denervation of skeletal muscles. Signs of muscle weakness and atrophy dominate the clinical presentation.[29,40,43,55] Weakness may occur acutely in horses with (common) or without (uncommon) noticeable muscle wasting. In 4 horses that developed EMND when fed a vitamin E-deficient diet, there was mean weight loss of 92 kg at the time signs of limb weakness occurred.[54] In rare cases, the atrophy may advance insidiously without sudden weakness. Typically, there is an acute onset of trembling in antigravity muscles, generalized sweating, and frequent episodes of recumbency. When standing in one place, horses with EMND adopt a characteristic "horse-on-a-ball" stance with the limbs gathered close together under the body[56] (Figure 19.3). Affected horses lack the strength necessary to engage the stay apparatus of the limbs when standing still; thus, they constantly shift weight between limbs and have great difficulty standing in a confined area such as a stocks. Acutely affected horses are more comfortable walking than standing although even brief walking exercise may cause signs of distress such as sweating, tachypnea, and nasal flaring. Typically, at the walk, protraction phases appear somewhat short and hypometric. Horses with EMND do not have signs of ataxia such



Figure 19.3. Characteristic gathering of feet under the body ("horse on a ball") in a horse with acutely presenting EMND. This 13-year-old Quarter Horse mare had been kept on a sand lot and fed bleached grass hay and sweet feed for the previous 10 years. There was sudden onset muscle trembling and recumbency 2 days before this photograph was taken.

as interference between limbs or circumduction of the pelvic limbs.

In most horses with EMND, the head is carried below the shoulders, usually reflecting obvious wasting of the neck muscles (Figure 19.4).[40] The tail head is elevated in many cases because of atrophy and contracture of the dorsal coccygeal muscles (Figure 19.5).[40] If not present at presentation, widespread muscle atrophy develops quickly (days to weeks) and is most obvious in the quadriceps, triceps, and gluteal areas.

Despite the frequent occurrence of pathologic changes in the motor nuclei of cranial nerves V and XII noticeable atrophy of the masseters or tongue has not been reported. The only clinical signs possibly ascribable to cranial nerve involvement are weak palpebral tone, dilated pupils, and sluggish pupillary light reflexes reported in a horse examined in the United Kingdom.[57]

In some 40% of cases, fundoscopic examination reveals a horizontal band of pigment above the optic disc at the tapetal-nontapetal junction (Figure 19.6).[40,50] The pigment may be brown-black to yellow-brown and has a reticulated or mosaic appearance. Surprisingly, problems with vision have not been reported even in EMND horses with severe pigment retinopathy.[50]

Laboratory Findings and Ancillary Testing

Available data for clinicopathologic testing of clinical and experimental cases of EMND are shown in (Table 19.1). Typical cases have below-range plasma/ serum vitamin E concentration. However, as a stand-alone test, vitamin E is quite nonspecific:[56]



Figure 19.4. Because of weakness of the neck muscles, the horse shown in Figure 19.4 spent most of its time either recumbent or with the head held below the withers.



Figure 19.5. Elevation of the tailhead in the horse shown in Figure 7.3.

Normal pasture mates of experimentally induced[54] or naturally occurring[43] EMND horses often also have low vitamin E. In healthy pasture-fed horses, vitamin E concentrations are variable during the day and often drop transiently below the normal range.[58] For this reason, it is recommended that plasma (or serum) from serial blood collections throughout the day be combined for the purpose of vitamin E assay.[58]

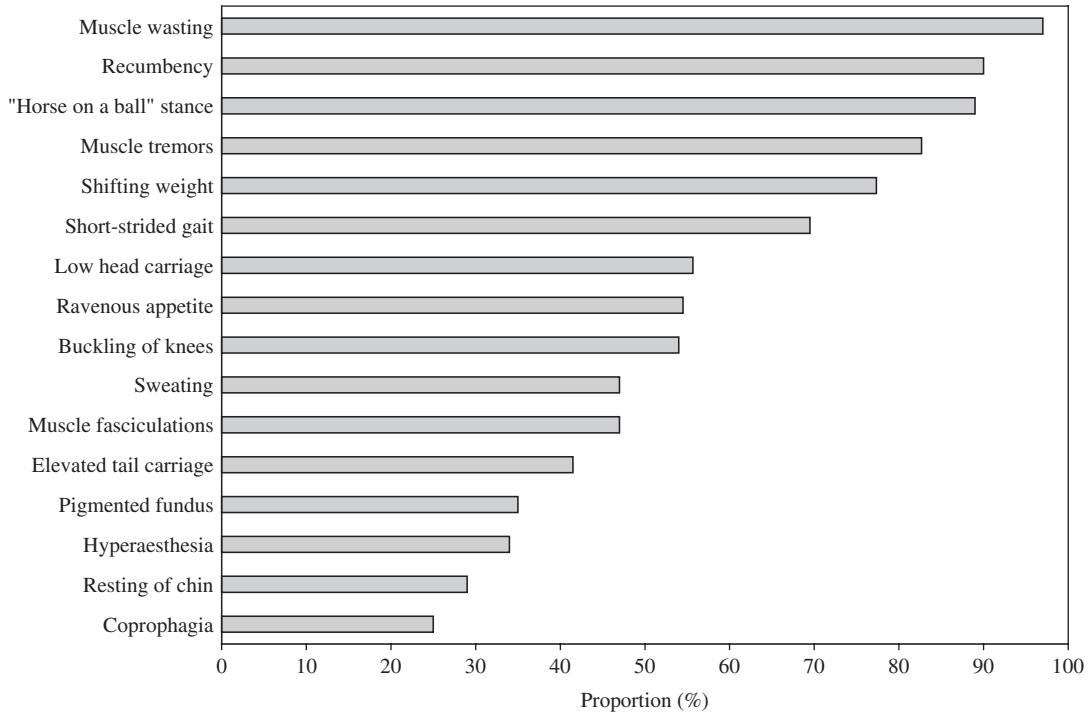


Figure 19.6. Aggregate frequency distribution of clinical signs in horses from 3 published case series (Refs. 12, 13, 15).

Mild to moderate increases in plasma or serum CK and AST activity are found during the initial rapid progression of clinical signs, but muscle enzyme activities may be normal in chronic stable cases (Table 19.1).

Changes in cytology of cerebrospinal fluid are not seen in EMND; however, there may be increased total protein concentration and CK activity (Table 19.1).[29,40,55] IgG index is high in many cases, suggesting the presence of intrathecally produced IgG.

Needle Electromyography

Needle electromyography (EMG) can be performed in the standing or recumbent, anesthetized horse. Horses with EMND often have abnormal EMG findings including prolonged insertional activity and pathologic spontaneous activity such as fibrillation potentials and trains of positive sharp waves.[56] Signs of denervation are found in facial muscles as well as in appendicular and epaxial muscles.[29] Standing EMG is preferred in order to avoid anesthesia in weak, compromised animals; however, interpretation of these studies is difficult because of movement artifacts associated with reluctance of affected horses to stand in one place. The use of sedation and caudal epidural anesthesia (lidocaine, 0.2 mg/kg) was reported to facilitate the procedure in a horse with EMND.[57] Techniques for quantitative analysis of motor action potentials have been published,[59] and results are abnormal in horses with EMND.[60] Regardless of the EMG technique used, abnormal results are nonspecific as to cause, suggesting only denervation or myopathy.[56]

Glucose Absorption/Metabolism

Oral glucose tolerance tests in horses with EMND were abnormal in approximately 50% of reported cases whereas results of oral xylose absorption tests were normal or slightly low.[40,43,60] Plasma glucose curves were lower than reference range in 6/8 horses given oral glucose and peak glucose concentrations were below normal range in 2/6 horses

Table 19.1. Clinico-Pathologic Parameters of Value in the Evaluation of Horses with Motor Neuron Disease

Source/Analyte		EMND	Normal[a] (Range/Control)	Reference
Plasma/Serum				
	Vitamin E (μg/mL)	0.255 ± 0.159	2.0 – 4.0 (R)	40
		0.4 – 1.5	2.0 – 4.4 (R)	41
		0.76 ± 0.70	2.15 ± 1.66 (C)	44
		0 – 1.22	0.108 – 2.56 (C)	43
	CK (U/L)	301 ± 365	<200 (R)	60
		875 – 3,820		48
		149 – 3,508		43
		482 – 9,303	143 – 531 (R)	46
	AST (U/L)	367 ± 169	<275 (R)	60
		538 – 974		48
	GGT (U/L)			
	LDH (U/L)	1160 ± 787	<420 (R)	60
Cerebrospinal fluid				
	TP (mg/dL)	17 – 166	0 – 90 (R)	43
		34 – 145	0 – 70 (R)	46
Serum/CSF				
	IgG index	0.1 – 9.7	<0.272 (R)	43,65

[a]Normal ranges (R) or controls (C) used in cited reference.
CK = creatine kinase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; TP = total protein.

given IV glucose.[60] On the basis of hyperglycemic clamp results in these horses, it was suggested that increased glucose metabolism, rather than reduced intestinal absorption, was the cause of abnormal oral glucose tolerance in horses with EMND.[61] Euglycemic clamp results from one horse showed a 5.4-fold increase in insulin sensitivity compared with control horses.[61]

Nerve Biopsy

Biopsy of the ventral branch of the spinal accessory nerve allows reliable antemortem diagnosis of EMND, at least in subacute and chronic cases.[29,62] A 5 cm section of the nerve is excised as it courses over and into the medial belly of the sternocephalicus muscle. The procedure can be performed either in the standing or recumbent, anesthetized patient and does not induce visible muscle atrophy at the surgical site. A positive histologic result is evidence of mild to severe Wallerian degeneration of axons and Schwann cell proliferation. Chronic cases are marked by loss of myelinated fibers, presence of compact Büngner's bands, and increased endoneurial collagen. For a group of pathologists ranging in experience from trainees to EMND experts, positive predictive value of nerve histology for EMND was 77.4% and negative predictive value was 90%.[62] False negative results appeared to be most likely in acute cases (<2 weeks). Nerve biopsy has largely been supplanted as an initial test by evaluation of sacrocaudalis dorsalis muscle biopsies.

Muscle Biopsy

The initial invasive procedure of choice is biopsy of the sacrocaudalis dorsalis tailhead muscle.[29,46,63] This muscle is rich in type I myofibers, a fiber type that is highly sensitive to the effects of denervation. The muscle sample is obtained under local anesthesia, placed on a tongue depressor, and sent chilled or in 10% formalin for histologic examination (Figure 19.7). There is neurogenic atrophy characterized by variable numbers of angular atrophied

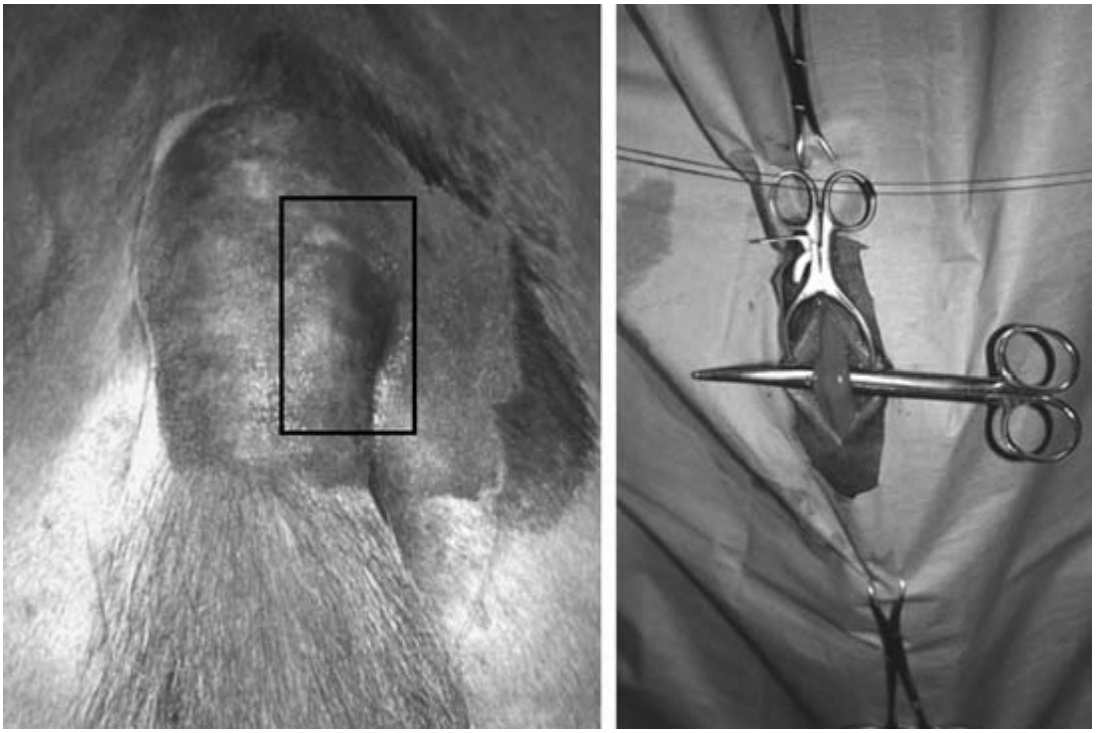


Figure 19.7. Location over the tailhead of biopsy site (rectangle in left image) and isolation, elevation, and removal of a section of the right sacrocaudalis dorsalis muscle (right).

fibers. Atrophied muscle fibers are of both types but type I fibers predominate. The use of muscle biopsy has high sensitivity for EMND (>90%) but relatively low specificity.[29] In chronic EMND cases, histology of nerve biopsy may have higher sensitivity for diagnosis than muscle histology.[29]

Diagnosis

Antemortem diagnosis of EMND usually is not difficult. It is based on typical clinical signs, age of 2 years or older, and diet low in green forage and high in carbohydrate. Needle EMG findings of denervation, especially in the deep limb muscles, are difficult technically because of movement artifact in weak horses but are supportive of the diagnosis as are mild to moderate increases in plasma CK and AST activity and low plasma vitamin E concentration. Finally, evidence of denervation in muscle or nerve biopsies in the context of the preceding clinical and laboratory findings is tantamount to a definitive diagnosis of EMND. Occasionally, in cases of insidiously progressive EMND, especially in nonendemic areas, diagnosis is only made postmortem.

Necropsy Findings

Although there is obvious weight loss in horses with EMND, fat deposits, noted postmortem, are usually within normal limits.[29,46,55,63] In acute cases, there is widespread degeneration and loss of somatic motor neurons in the ventral horns of the spinal cord accompanied by degenerative axonal changes in the ventral roots and peripheral nerves. All brainstem cranial nerve somatic motor nuclei, except those of cranial nerves III, IV, and VI, are variably involved. Most affected neurons are swollen, markedly chromatolytic and diffusely argyrophilic while severely affected neurons are shrunken or vacuolated.[46] In chronic "burnout" cases, there are glial scars consisting of astrocytes and lipofuscin-laden microglia.[29] Additional deposits of ceroid lipofuscin are found in the retinal epithelium and occasionally in the liver and intestine.[40] Relatively minor neurodegenerative

changes may be found in dorsal root ganglia.[46] In contrast to grass sickness, there are minimal or no lesions in the autonomic nervous system. In skeletal muscles, there is angular atrophy of all myofiber types with some selectivity for type I fibers.[48] Atrophied fibers are intermingled among normal fibers and fascicles. Involvement of the deeper muscles of the limbs may be grossly evident as pale discoloration.

Treatment

The only treatment recommended for horses with EMND is vitamin E supplementation. This can be supplied in good quality grass and alfalfa hay or by vitamin E supplementation (at least 10 U/kg). Natural vitamin E (RRR-α-tocopherol) has higher bioavailability and potency than synthetic vitamin E (*all-rac*-α-tocopherol acetate).[64] While vitamin E treatment appears logical, there has been no clinical trial that has evaluated the efficacy of treatment.

In light of the clinical observation that many EMND horses have increased appetite,[29,41,55] it is interesting that one series of cases was noted to have increased glucose metabolism possibly associated with increased insulin sensitivity.[60,61] Also, likely associated with altered glucose metabolism is the observation of transformation of skeletal muscle from oxidative (slow twitch) to glycolytic (fast twitch) phenotype in horses with EMND.[48] On the basis of these results, Wijnberg[56] has calculated that the daily caloric intake of affected horses could be doubled. Thus, as part of the convalescent program of surviving horses, high quantity and quality of pasture, hay, and concentrate is recommended.

Clinical Course

According to Divers *et al.*,[40] within 6 weeks after onset of signs, approximately 40% of horses progressively deteriorate and are euthanized while a similar number undergo marked improvement in clinical signs (usually following relocation to another premise and/or administration of antioxidants). These "recovered" horses look normal but may recrudesce under the pressure of intensive training or competition.[29] In the remaining 20%, the disease appears to "burn out" and such horses survive with permanent and obvious muscle wasting and emaciation.

EQUINE GRASS SICKNESS

History and Epidemiology

Grass sickness is a fatal dysautonomia of equids typically associated, as the name suggests, with full-time access to pasture. The condition was first recorded in army remount horses in 1905 at Barry Camp, Montrose, Scotland, and by 1909 had occurred in outbreak form in Eastern Scotland.[66,67] In retrospect, the disease probably occurred during the latter part of the 19th century.[67] It has been suggested that the initial cases followed the importation of Peruvian guano (bird droppings) for application to fields as fertilizer.[68] Equine dysautonomia has long been recognized in the Patagonia region of South America where it is known as "mal seco."[69] In the years after its first recognition in Scotland, the geographic range of the disease expanded rapidly until 10–20% of the working horses in Scotland were affected. This suggested the introduction of a novel infectious disease.[70] By 1922, cases of equine grass sickness (EGS) were seen in horses in the Salisbury Plain area of England.[67] EGS remains endemic in Scotland, England, and Wales and has also been reported from continental Europe, the Falkland islands, and Colombia with isolated cases in Australia and the United States.[68] International attention was focused on the disease after the death of the prominent Thoroughbred stallion Dubai Millenium[68] from EGS.

Epidemiological studies of EGS in Scotland in the early 1970s identified full-time grazing, a recent change in pasture or premises, previous occurrence of the disease on the premises, lack of hay in the diet, and good bodily condition as risk factors.[71,72] A later case-control study recruited EGS cases and on-farm or local control horses from throughout the United Kingdom.[73] Although cases occurred in every month of the year, the study confirmed the seasonal nature of EGS, with peak numbers between April and June. The risk of disease was highest in horses aged 3–5 years although cases have been reported in horses from 10 months to 20 years of age. This study strengthened the association with full-time grazing, change of pasture, and previously affected premises. Interestingly, the risk of EGS declined proportionally with time since the last case or last change of pasture. Novel findings included a 10-fold reduction in risk for horses in contact with previous cases and a 3-fold higher risk for males compared with females.

A time-matched study designed to account for the effects of season on premise-level risk utilized histologically confirmed cases referred to the University of Liverpool.[74,75] In the final multivariable model, EGS on a particular premise was strongly associated with previous cases on that premise, pasture disturbance (e.g., construction, mole activity), and high nitrogen content of soil (not pasture). Although cases often are associated with cool dry conditions and the presence of ground frost, no meteorological variable was associated with EGS risk. However, it was suggested that the spatial and temporal clustering documented for EGS cases in England and Wales could be explained either by a contagious process or by local climate and/or pasture management practices.[74] At the horse level, feed change in the previous 14 days and recent dewormings with ivermectin were significant positive risk factors for EGS in the multivariable model while daily feeding of hay or haylage significantly reduced the risk of EGS.[75] Another study compared premises with recurrent EGS with those that had a single, unprecedented EGS incident.[76] This comparison revealed that high horse numbers, predominance of young horses, sandy or loamy soils, and mechanical removal of feces were premise-level risk factors. Chalky soil, manual removal of feces from pastures, pasture grass mowing, and co-grazing with ruminants were protective factors associated with lower recurrence rates for EGS.

In recent years, there has been interest in the possible role of toxicoinfectious botulism due to *Clostridium botulinum* type C in the pathogenesis of EGS. This is discussed in detail in the next section. In support of the botulism hypothesis, the botulinum neurotoxin BoNT/C was detected, directly or after enrichment procedures, in the ileal contents or feces of EGS horses at significantly higher rates than was the case for control horses.[77] Toxin was detected in 74% of acute EGS cases, 67% of subacute cases, and 67% of chronic cases. Only 10% of control horses tested positive.[77] Horses with EGS were found to have significantly lower concentration of serum IgG reactive with BoNT/C or clostridial surface antigens than was the case for in-contact horses or pasture mates.[78] In a similar study that was adjusted for age categories, risk for each of the EGS categories (acute, subacute, chronic) was negatively associated with serum antitoxin or anti-clostridial antibody concentration.[79]

Etiology and Pathogenesis

Theories as to the cause of EGS have included mineral or vitamin deficiencies or exposure to toxic plants, secondary metabolites in pasture grass, insects, mycotoxins, viruses, or bacterial toxins.[70,80] Although the clinical syndrome of EGS has not been reproduced experimentally, the characteristic neuropathology has been induced by administration of serum from acute cases into the peritoneal cavity or parotid salivary gland.[81,82] The activity was found in a >30-kD fraction of serum but was not further characterized.

The distribution of degenerative lesions in the enteric nervous system has been explained either as systemic hematogenous or axonal transport of a neuronal toxin.[83] The distribution and character of lesions fits best with the hypothesis that there is a primary intestinal lesion with retrograde axonal transport of neurotoxin or secondary degeneration.[80] The observed absence of lesions in the dorsal root ganglia can be explained in this way.

Recently, evidence has been gathering that EGS is a toxicoinfectious botulism comparable to infantile botulism of humans and "shaker foal" syndrome.[77] Exotoxins of *Clostridium perfringens* type A have been suggested as a cause of EGS in Colombia, but there was no evidence of this in Scotland.[84] The botulism hypothesis was initially offered in 1919 after presumptive *C. botulinum* was isolated postmortem from the intestine or spleens of EGS horses.[66,68] Some similarities were noted between the clinical signs of EGS and botulism. Vaccine trials conducted in 1922 and 1923 with an antitoxin-neutralized toxin vaccine produced promising results and led to a commercial antiserum product for the treatment/prevention of EGS;[66] however, the botulism theory proved controversial and was subsequently abandoned in favor of a short-lived streptococcal theory.

In the 1990s, the possible role of *C. botulinum* was reconsidered and a hypothesis developed that EGS was a toxicoinfectious form of botulism involving a type C strain commonly carried by birds.[77] Strong support for this hypothesis has been (1) the demonstrated association between EGS and the presence in ileal contents of *C. botulinum* type C and type C1 neurotoxin (BoNT/C);[77] (2) the observation that horses with EGS have significantly lower serum antibodies to *C. botulinum* and BoNT/C than do pasturemate controls;[78,79] and (3) presence of rising titers of specific IgG antitoxin in chronic EGS cases.

C. botulinum type C is unique among clostridial organisms in that its major toxin, BoNT/C, possesses potent and nonspecific neurotoxicity in vitro, probably via action on cellular syntaxin.[77] Toxins C2 and C3 also may contribute to the neurotoxicity of *C. botulinum* type C. It has been hypothesized that toxin production and absorption occur in the ileum due to overgrowth from normal intestinal flora and/or spore germination in association with a *nutritional trigger*.[68] Factors such as changes in feed, pasture, and weather conditions and parasite status are proposed to contribute to changes in flora favoring clostridial growth. According to this hypothesis, the effects of neurotoxin production would then be dependent on factors such as age, previous exposure, presence of neutralizing antibody, and antioxidant status and may lead to neurotoxicosis and the signs of EGS.

It should be noted that despite extensive correlative evidence of its involvement in EGS, a causal association of *C botulinum* and EGS has not yet been demonstrated.

Clinical Signs

The major clinical signs of grass sickness reflect dysfunction of the autonomic nervous system, particularly of the gastrointestinal tract.[80,83,85] There is dysphagia, gastric and small intestinal dilation, nasogastric reflux, colonic impaction, and colic.

Clinical presentations are classified as acute (course of less than 48 hours), subacute (2–7 days) and chronic (greater than 7 days).[86]

Acutely affected horses may be found dead or in abdominal crisis. There are signs of colic, tachycardia, generalized sweating, nasogastric reflux including spontaneous nasal regurgitation of stomach contents, absence of intestinal borborygmi, and abdominal distension. Rectal palpation and transabdominal ultrasonography reveal distended loops of small intestine and gas-filled large bowel. Affected horses are unable to swallow food or water and thick ropy saliva may drool from the mouth. Fine muscle fasciculations similar to those seen with EMND may affect the triceps and quadriceps.

Horses with subacute EGS survive long enough to develop colonic impactions and secondary large intestinal tympany.

Chronic EGS may develop insidiously and only a minority of these cases shows mild, intermittent colic. There is patchy sweating and/or piloerection on the neck, flanks, and behind the shoulders. (Figure 19.8) Typically, the appetite is reduced and there are varying degrees of difficulty in chewing and swallowing; however, salivation, accumulation of fluid in the stomach, and impaction are not usual features. There is often bilateral ptosis with ventral deviation of the eyelashes secondary to loss of sympathetic eyelid tone. Because of suppression of normal nasal secretions, there is a characteristic dry crusty nasal exudate (rhinitis sicca). Fecal production is reduced, and feces are unusually firm and small. There is rapid and severe weight loss which may culminate in obtundation, emaciation, and death.



Figure 19.8. Horse with chronic EGS showing patchy sweating around the neck and residues of salt elsewhere on the body reflecting previous sweating. Image courtesy of Dr. IG Mayhew.

Acute and subacute cases are invariably fatal. Death occurs from gastric rupture, circulatory compromise, cardiopulmonary failure, or most commonly from euthanasia. Before the 1980s, it was thought that chronic EGS also was usually fatal or associated with hopeless emaciation. Histologically confirmed EGS has never been documented to recur in recovered horses.[76]

Laboratory Findings and Ancillary Tests

There is no confirmatory blood test for EGS. Nonspecific abnormalities are consistent with severe dehydration, hypovolemia, stress, loss of GI secretions, and anorexia.[87] Peritoneal fluid protein concentration may be high although nucleated and red cell counts usually are normal. Serum concentrations of numerous acute phase protein, including α-2 macroglobulin, ceruloplasmin, haptoglobin, and orosomucoid, are high, but such assays are not readily available.[88]

Ileal Biopsy

A full-thickness ileal biopsy is obtained during exploratory celiotomy and is examined histologically for characteristic histologic changes to nerve plexi.[74] This technique is highly sensitive and specific for diagnosis of grass sickness.

Rectal Biopsy

A preliminary report showed that the presence of three chromatolytic neurons/rectal biopsy section as a criterion for diagnosis of EGS gave a sensitivity of 71% and specificity of 100%, suggesting that this procedure may have value as an antermortem diagnostic test.[89]

Barium Swallow

Radiography after oral or intraesophageal administration of barium shows abnormal esophageal motility and pooling of contrast media in the distal esophagus.[90] The procedure is now seldom used in the diagnosis of EGS.

Needle Electromyography

A technique for quantitative EMG in horses has been described.[91] Using this technique, pathological spontaneous activity was observed in the skeletal muscle of 12 horses with EGS, although these changes were subtle.[92]

Phenylephrine Test

In EGS cases with ptosis, topical application of 0.5 mL of 0.5% phenylephrine eyedrops results in normalization of the eyelash angle and is supportive of the diagnosis[93] (Figure 19.9).

Diagnosis

Diagnosis is based on typical clinical signs, age of animals, recent change of grazing, and a history of previous disease on the premises and/or paddock. Rhinitis sicca is regarded as almost pathognomonic for chronic EGS, and a positive response to the eyelid phenylephrine test provides strong supportive evidence for the diagnosis. Definitive antemortem diagnosis requires examination of an ileal biopsy although rectal biopsy results may provide strong supportive evidence.[68] Demonstration of characteristic histologic changes in enteric plexuses and ganglia provides definitive diagnosis postmortem.

Treatment and Prevention

In horses with acute or subacute EGS, treatment is ineffective. Treatment of selected chronic cases involves excellent nursing care and provision of palatable, easily swallowable food and high energy concentrates.[94] Clinical recovery, which occurs in about 50% of pre-selected treated cases, takes approximately 6–8 weeks.

In light of the putative causal association between *C. botulinum* type C and EGS, there is great interest



Figure 19.9. Phenylephrine test in horse with EGS. 0.5 ml of 0.5% phenylephrine has been applied to the right eye. Note the elevation of the eyelid in the treated eye. Image courtesy of Dr. IG Mayhew.

in the development of vaccines;[76] testing of candidate products should begin within the next several years.

Current efforts at prevention involve minimization of known risk factors and introduction of suspected protective practices.[95] Thus, in endemic areas, horse owners are advised to avoid exposure to pastures where previous cases have occurred, minimize disturbance of pasture or soil, prevent overgrazing of pasture, and avoid the "overuse" of ivermectin dewormers. On the other hand, owners are encouraged to co-graze horses with ruminants, mow pastures regularly, remove feces by hand, and supplement pasture feeding with hay or haylage. These practices are particularly important during seasonal and climatic risk periods and for young horses in good bodily condition, especially those recently imported.

Necropsy Findings

Gross necropsy findings in horses with EGS include esophageal ulceration, fluid distension of the stomach and small intestines, impaction of the large colon and/or cecum, and the presence of inspissated mucus within the small colon and rectum. Subacute and chronic cases do not have gastric and small intestinal distension but do have variable degrees of large intestinal impaction and often rhinitis sicca.[83]

Histologic lesions of neuronal degeneration are most evident in the autonomic ganglia, gut wall nerve plexuses, brain, and spinal cord.[96-98] There is chromatolysis, nuclear eccentricity, nuclear degenerative changes, cell death and neuronophagia, cytoplasmic vacuolation, and spheroid formation.[99] Lesions are most evident in prevertebral (celiacomesenteric, cranial mesenteric, caudal mesenteric) and paravertebral (stellate, cranial cervical, caudal cervical, thoracic sympathetic chain) ganglia of the autonomic nervous system and enteric neurons (myenteric and submucous plexuses).[85] Lesions are also found in autonomic and somatic cranial nerve nuclei (particularly those of cranial nerves III, V, VI, and V and X) and in the intermediolateral and ventral horns of the spinal cord grey matter.[86]

CEREBELLAR DEGENERATION

The most commonly reported cerebellar neurodegenerative conditions of horses are cerebellar abiotrophies of Arab[100] and Gotland pony foals.[101] These are suspected to be familial conditions with autosomal recessive modes of inheritance. A distinct apparently inherited cerebellar condition of Oldenberger foals is characterized by multifocal cerebellar degeneration and an invariably fatal outcome.[101] A syndrome of progressive ataxia associated with cerebellar degeneration was identified in one American Miniature Horse foal, and anecdotal evidence for an additional two cases was cited.[102] In contrast to cerebellar abiotrophy of Arabians, the condition in the Miniature foal involved cavitation of the olivary and lateral cuneate nuclei and the putamen. It was suggested that the medullary lesions may reflect retrograde transynaptic degeneration as both nuclei have direct synaptic connections to the cerebellar cortex.

Cerebellar degeneration and lipofuscin accumulation associated with presumed toxicosis has been described in Gomen disease of horses in New Caledonia.[103,104] Induced mannosidosis with neurovisceral degeneration involving the cerebellum has been reported for swainsonine toxicity of horses in the US ("locosim" caused by ingestion of *Astragalus* or *Oxytropis* spp. plants),[105] Australia (*Swainsonia* spp.),[106] and Brazil (*Sida carpinifolia*).[107] These are further discussed in Chapter 26.

CEREBELLAR ABIOTROPHY

The term abiotrophy refers to spontaneous premature degeneration resulting from an inborn error of development.[108] Syndromes of cerebellar abiotrophy (CA) have been described for Arab,[100] part-Arab,[101,109] and Gotland Pony[101] foals. In affected Arab foals, degeneration begins after formation of the cerebellum and is characterized by apoptosis of Purkinje cells.[110] The mode of inheritance is generally speculated to be simple autosomal recessive;[100,101,111,112,113] however, because the syndrome has been confirmed in part-Arabs and a marked preponderance of males (17/21) was found in one case series,[111] inheritance of CA warrants further investigation. The Veterinary Genetics Laboratory at the University of California, Davis is currently soliciting cases of CA for breeding studies and development of genetic tests.[113]

Foals may be affected at birth or may be born normal with onset of signs sometime during the first year of life. In 18 confirmed or suspected cases for which individual data were reported,[101,109,112,114]

9 were male and 9 were female. By contrast, for another reported series of 21 cases, 17 were male.[111] Among the 18 cases cited above, signs were present at birth in 4 (22%), began at ⩽3 months of age in 10 (56%), 3–6 months in 2 (11%), and >6 months in 2 (11%). Fifteen were purebred Arabs, one was three-quarter Arabs, and 2 were half-Arab foals.

Usually the first signs noticed are incoordination, base-wide posturing in the thoracic limbs, and head tremors. The head tremor usually is a coarse bobbing in either the horizontal or vertical plane. When the head is extended (e.g., toward the dam's udder or toward offered food), the head tremor becomes more pronounced. Although foals can see normally, the menace response cannot be elicited in most foals. Although there clearly is cerebellar involvement in a competent menace response, the neuroanatomy of this involvement is not completely understood. Other signs of cranial nerve dysfunction are not seen in foals with CA.

Foals walk with a swaying, lurching gait and may even wobble side to side or back and forth while standing still. Thoracic limbs may appear stiff, or there may be exaggerated flexion during the protraction phase of walking. Gait abnormalities are most obvious when movement is initiated and during turns. Normal strength is preserved even in severely ataxic foals, and blindfolding does not exacerbate clinical signs. All clinical signs are exaggerated by stimulation of affected foals. Such hyperresponsiveness means CA foals are difficult to halter-train and lead; even normal handling often causes an affected foal to pull away or even flip over backwards.

Definitive laboratory diagnosis of CA is not yet possible. Hematologic and serum chemistry findings are usually normal. Evaluation of CSF usually is unremarkable although some foals have high CSF protein concentration and CK activity, consistent with active neurodegeneration at the time of CSF collection.[112] It is likely that magnetic resonance,

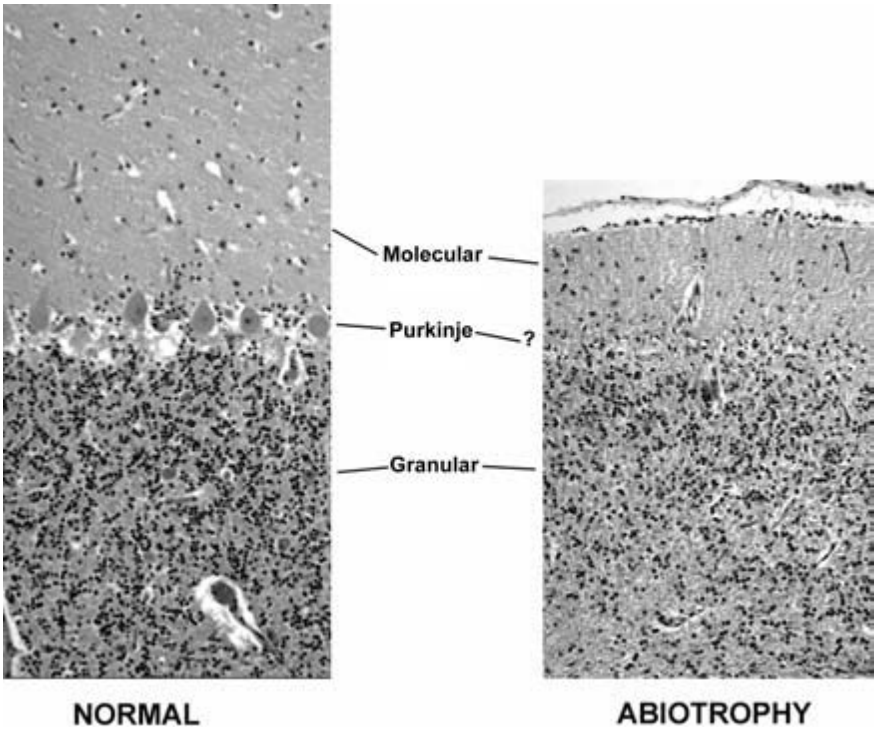


Figure 19.10. Cross-section of the cerebellar cortex from normal foal and foal with cerebellar abiotrophy. Note the thinning of the molecular layer, absence of Purkinje cells, and decreased cellularity of the granular layer in the CA specimen.

and possibly computed tomography, imaging of affected foals would reveal abnormality of the cerebellum in foals with CA, but such evaluation has not yet been reported.

Signs may be stable after onset or get worse for up to several months. It is rare, however, for CA foals to become recumbent. Modest improvement has been noted in some mildly affected horses once they become adults.[101] Foals with CA seldom succumb to direct effects of the condition, but most are euthanized because of severe clinical signs and poor prognosis.

Gross appearance of the affected brain is usually described as normal; however, the ratio of cerebellar to whole brain weight is usually $<8\%$ while normal ratios are $\geqslant 8\%$. The characteristic histologic lesion is thinning of the cerebellar cortex affecting both granular and molecular layers.[100,101,109,111,112,114] There is marked reduction in the number of Purkinje cells in the granular layer, and some of those remaining show degenerative changes (swelling, shrinkage and hyperchromasia of the perikaryon). There is relative sparing of the Purkinje cells of the nodulus and flocculi.[112] Vacuolation may be noted in the olivary nuclei.[109] Mineralized neuronal cell bodies may be found in the thalamus adjacent to the third ventricle (Figure 19.10).

REFERENCES

1. Mayhew IG, deLahunta A, Whitlock RH. 1976. Equine degenerative myeloencephalopathy. *Proc Annual Meeting Am Assoc Equine Pract* 22: 103–5.
2. Mayhew IG, deLahunta A, Whitlock RH, *et al*. 1977. Equine degenerative myeloencephalopathy. *J Am Vet Med Assoc* 170:195–201.
3. Scarratt WK, Saunders GK, Sponenberg DP, *et al*. 1985. Degenerative myelopathy in two equids. *Equine Vet Sci* 5:139–41.
4. Mayhew IG, de Lahunta A, Whitlock RH, *et al*. 1978. Spinal cord disease in the horse. *Cornell Vet* 68 (Suppl. 6):24–35.
5. Dill SG, Correa MT, Erb HN, *et al*. 1990. Factors associated with the development of equine degenerative myeloencephalopathy. *Am J Vet Res* 51:1300–5.
6. Blythe LL, Hultgren BD, Craig AM, *et al*. 1991. Clinical, viral, and genetic evaluation of equine degenerative myeloencephalopathy in a family of Appaloosas. *J Am Vet Med Assoc* 198:1005–13.
7. Mayhew IG, Brown CM, Stowe HD, *et al*. 1987. Equine degenerative myeloencephalopathy: a vitamin E deficiency that may be familial. *J Vet Intern Med* 1: 45–50.
8. Beech J. 1987. Equine degenerative myeloencephalopathy. In *Current therapy in equine medicine*, edited by Robinson, NE, 353–5. Philadelphia: W.B. Saunders.
9. Blythe LL, Craig AM. 1992. Equine degenerative myeloencephalopathy. Part I. Clinical signs and Pathogenesis. *Compend Contin Educ Pract Vet* 14:1215–21.
10. Baumgartner W, Frese K, Elmadfa I. 1990. Neuroaxonal dystrophy associated with vitamin E deficiency in two Haflinger horses. *J Comp Pathol* 103:114–9.
11. Gandini G, Fatzer R, Mariscoli M, *et al*. 2004. Equine degenerative myeloencephalopathy in five Quarter Horses: clinical and neuropathological findings. *Equine Vet J* 36:83–5.
12. Beech J. 1984. Neuroaxonal dystrophy of the accessory cuneate nucleus in horses. *Vet Pathol* 21:384–93.
13. Beech J, Haskins M. 1987. Genetic studies of neuroaxonal dystrophy in the Morgan. *Am J Vet Res* 48:109–13.
14. deLahunta A. 1990. Abiotrophy in domestic animals: a review. *Can J Vet Res* 54:65–76.
15. Montali RJ, Bush M, Sauer RM, *et al*. 1974. Spinal ataxia in zebras. Comparison with the wobbler syndrome of horses. *Vet Pathol* 11:68–78.
16. Liu SK, Dolensek EP, Adams CR, *et al*. 1983. Myelopathy and vitamin E deficiency in six Mongolian wild horses. *J Am Vet Med Assoc* 183:1266–8.
17. Dill SG, Kallfelz FA, deLahunta A, *et al*. 1989. Serum vitamin E and blood glutathione peroxidase values of horses with degenerative myeloencephalopathy. *Am J Vet Res* 50:166–8.
18. Craig AM, Blythe LL, Lassen ED, *et al*. 1989. Variations of serum vitamin E, cholesterol, and total serum lipid concentrations in horses during a 72-hour period. *Am J Vet Res* 50:1527–31.
19. Harding AE, Muller DP, Thomas PK, *et al*. 1982. Spinocerebellar degeneration secondary to chronic intestinal malabsorption: a vitamin E deficiency syndrome. *Ann Neurol* 12:419–24.
20. Sokol RJ, Guggenheim MA, Iannaccone ST, *et al*. 1985. Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. *N Engl J Med* 313:1580–86.
21. Rosenblum JL, Keating JP, Prensky AL, *et al*. 1981. A progressive neurologic syndrome in children with chronic liver disease. *N Engl J Med* 304:503–8.
22. Nelson JS. 1983. Neuropathological studies of chronic vitamin E deficiency in mammals including humans. *Ciba Found Symp* 101:92–105.

23. Nelson JS, Fitch CD, Fischer VW, *et al*. 1981. Progressive neuropathologic lesions in vitamin E-deficient rhesus monkeys. *J Neuropathol Exp Neurol* 40:166–86.
24. Cavalier L, Ouahchi K, Kayden HJ, *et al*. 1998. Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. *Am J Hum Genet* 62:301–10.
25. Blythe LL, Craig AM, Lassen ED, *et al*. 1991. Serially determined plasma alpha-tocopherol concentrations and results of the oral vitamin E absorption test in clinically normal horses and in horses with degenerative myeloencephalopathy. *Am J Vet Res* 52:908–11.
26. Sokol RJ, Butler-Simon NA, Bettis D, *et al*. 1987. Tocopheryl polyethylene glycol 1000 succinate therapy for vitamin E deficiency during chronic childhood cholestasis: neurologic outcome. *J Pediatr* 111:830–6.
27. Craig AM, Blythe LL, Rowe KE, *et al*. 1991. Evaluation of the oral vitamin E absorption test in horses. *Am J Vet Res* 52:912–6.
28. Blythe LL, Craig AM. 1992. Equine degenerative myeloencephalopathy. Part II. Diagnosis and treatment. *Compend Contin Educ Pract Vet* 14:1633–7.
29. Divers TJ, Mohammed HO, Cummings JF. 1997. Equine motor neuron disease. *Vet Clin North Am Equine Pract* 13:97–105.
30. de la Rúa-Domènech R, Mohammed HO, Cummings JF, *et al*. 1997. Intrinsic, management, and nutritional factors associated with equine motor neuron disease. *J Am Vet Med Assoc* 211:1261–7.
31. Hahn CN, Mayhew IG. 1993. Does equine motor neuron disease exist in the United Kingdom? *Vet Rec* 132:133–4.
32. Proudman CJ, Knottenbelt DC, Edwards GB. 1993. Equine motor neuron disease. *Vet Rec* 132:198–9.
33. Lofstedt J, Ikede BO. 1994. Motor neuron disease in a quarter horse from Nova Scotia. *Can Vet J* 35:507–9.
34. Prendergast M, Bassett HF, Cummings JF. 1994. Equine motor neuron disease. *Vet Rec* 135:416.
35. Gerber H. 1994. Equine motor neuron disease and grass sickness [letter]. *Vet Rec* 135:440.
36. Sustronck B, Deprez P, van Roy M, *et al*. 1993. Equine motor neuron disease: the first confirmed cases in Europe. *Vlaams Dirgeneeskundig Tijdschrift* 62:40–4.
37. Kuwamura M, Iwaki M, Yamate J, *et al*. 1994. The first case of equine motor neuron disease in Japan. *J Vet Med Sci* 56:195–7.
38. Amorin RM, Kuchembuck MRG, Goncalves RC, *et al*. 1996. Doença do neurônio motor dos eqûinos: relato dos premeiros casos na América do Sul. *Braz J Vet Res Anim Sci* 33:47–52.
39. Gruys E, Beynen AC, Binkhorst GJ, *et al*. 1994. [Neurodegenerative disorders of the central nervous system in horses]. *Tijdschr Diergeneeskd* 119:561–7.
40. Divers TJ, Modhammed HO, Hintz HF, *et al*. 2006. Equine motor neuron disease: a review of clinical and experimental studies. *Clin Tech Equine Pract* 5:24–9.
41. McGorum BC, Mayhew IG, Amory H, *et al*. 2006. Horses on pasture may be affected by equine motor neuron disease. *Equine Vet J* 38:47–51.
42. Mohammed HO, Cummings JF, Divers TJ, *et al*. 1993. Risk factors associated with equine motor neuron disease: a possible model for human MND. *Neurology* 43:966–71.
43. Divers TJ, Mohammed HO, Cummings JF, *et al*. 1994. Equine motor neuron disease: findings in 28 horses and proposal of a pathophysiological mechanism for the disease. *Equine Vet J* 26:409–15.
44. de la Rúa-Domènech R, Mohammed HO, Cummings JF, *et al.* 1997. Association between plasma vitamin E concentration and the risk of equine motor neuron disease. *Vet J* 154:203–13.
45. Syrjä P, Cizinauskas S, Sankari SM, *et al*. 2006. Equine motor neuron disease (EMND) in a horse without vitamin E deficiency: a sequala of iron excess? *Equine Veterinary Education* 18: 158–63.
46. Cummings JF, De Lahunta A, George C, *et al*. 1990. Equine motor neuron disease: a preliminary report. *Cornell Vet* 80:357–79.
47. Rowland LP. 1994. Amyotrophic lateral sclerosis: theories and therapies. *Ann Neurol* 35:129–30.
48. Palencia P, Quiroz-Rothe E, Rivero JL. 2005. New insights into the skeletal muscle phenotype of equine motor neuron disease: a quantitative approach. *Acta Neuropathol (Berl)* 109:272–84.
49. Rowland LP. 1994. Amyotrophic lateral sclerosis: theories and therapies. *Ann Neurol* 35:129–30.
50. Riis RC, Jackson C, Rebhun W, *et al*. 1999. Ocular manifestations of equine motor neuron disease. *Equine Vet J* 31:99–110.
51. Divers TJ, De Lahunta A, Hintz HF, *et al*. 2002. Equine motor neuron disease - Update. *Proc 20th Annual Meeting ACVIM*, 15.
52. de la Rúa-Domènech R, Wiedmann M, Mohammed HO, *et al*. 1996. Equine motor neuron disease is not linked to Cu/Zn superoxide dismutase mutations: sequence analysis of the equine Cu/Zn superoxide dismutase cDNA. *Gene* 178:83–8.

53. Polack EW, King JM, Cummings JF, *et al*. 2000. Concentrations of trace minerals in the spinal cord of horses with equine motor neuron disease. *Am J Vet Res* 61:609–11.
54. Divers TJ, Cummings JE, De Lahunta A, *et al*. 2006. Evaluation of the risk of motor neuron disease in horses fed a diet low in vitamin E and high in copper and iron. *Am J Vet Res* 67:120–6.
55. Divers TJ, Mohammed HO, Cummings JF, *et al*. 1992. Equine motor neuron disease: a new cause of weakness, trembling, and weight loss. *Compend Contin Educ Pract Vet* 14:1222–6.
56. Wijnberg ID. 2006. Clinical Commentary: equine motor neuron disease. *Equine Vet Educ* 8:163–7.
57. Kyles KW, McGorum BC, Fintl C, *et al*. 2001. Electromyography under caudal epidural anaesthesia as an aid to the diagnosis of equine motor neuron disease. *Vet Rec* 148:536–8.
58. Blythe LL, Craig AM, Lassen ED, *et al*. 1991. Serially determined plasma alpha-tocopherol concentrations and results of the oral vitamin E absorption test in clinically normal horses and in horses with degenerative myeloencephalopathy. *Am J Vet Res* 52:908–11.
59. Wijnberg ID, Back W, de Jong M, *et al*. 2004. The role of electromyography in clinical diagnosis of neuromuscular locomotor problems in the horse. *Equine Vet J* 36:718–22.
60. Benders NA, Dyer J, Wijnberg ID, *et al*. 2005. Evaluation of glucose tolerance and intestinal luminal membrane glucose transporter function in horses with equine motor neuron disease. *Am J Vet Res* 66:93–9.
61. van der Kolk JH, Rijnen KE, Rey F, *et al*. 2005. Evaluation of glucose metabolism in three horses with lower motor neuron degeneration. *Am J Vet Res* 66:271–6.
62. Jackson CA, De Lahunta A, Cummings JF, *et al*. 1996. Spinal accessory nerve biopsy as an ante mortem diagnostic test for equine motor neuron disease. *Equine Vet J* 28:215–9.
63. Valentine BA, De Lahunta A, George C, *et al*. 1994. Acquired equine motor neuron disease. *Vet Pathol* 31:130–8.
64. Cummings JF, De Lahunta A, Summers BA, *et al*. 1993. Eosinophilic cytoplasmic inclusions in sporadic equine motor neuron disease: an electron microscopic study. *Acta Neuropathol (Berl)* 85:291–7.
65. Andrews FM, Maddux JM, Faulk D. 1991. Total protein, albumin quotient, IgG and IgG index determinations for horse cerebrospinal fluid. *Prog vet Neurology* 1:197–204.
66. Tocher JF, Tocher JW, Brown W, *et al*. 1923. Grass sickness investigation report. *Vet Rec* 3:37–45.
67. Miller K. 2005. Equine grass sickness fund: grass sickness and botulism. Retrieved on Sept 30, 2006 from http://www.grasssickness.org.uk.
68. Hedderson EJ, Newton JR. 2004. Prospects for vaccination against equine grass sickness. *Equine Vet J* 36:186–91.
69. Uzal FA, Robles CA. 1993. Mal seco, a grass sickness-like syndrome of horses in Argentina. *Vet Res Commun* 17:449–57.
70. McCarthy HE, Proudman CJ, French NP. 2001. Epidemiology of equine grass sickness: a literature review (1909–1999). *Vet Rec* 149:293–300.
71. Gilmour JS, Jolly GM. 1974. Some aspects of the epidemiology of equine grass sickness. *Vet Rec* 95:77–81.
72. Doxey DL, Gilmour JS, Milne EM. 1991. A comparative study of normal equine populations and those with grass sickness (dysautonomia) in eastern Scotland. *Equine Vet J* 23:365–9.
73. Wood JL, Milne EM, Doxey DL. 1998. A case-control study of grass sickness (equine dysautonomia) in the United Kingdom. *Vet J* 156:7–14.
74. French NP, McCarthy HE, Diggle PJ, *et al*. 2005. Clustering of equine grass sickness cases in the United Kingdom: a study considering the effect of position-dependent reporting on the space-time K-function. *Epidemiol Infect* 133:343–8.
75. McCarthy HE, French NP, Edwards GB, *et al*. 2004. Why are certain premises at increased risk of equine grass sickness? A matched case-control study. *Equine Vet J* 36:130–4.
76. Newton JR, Hedderson EJ, Adams VJ, *et al*. 2004. An epidemiological study of risk factors associated with the recurrence of equine grass sickness (dysautonomia) on previously affected premises. *Equine Vet J* 36:105–12.
77. Hunter LC, Miller JK, Poxton IR. 1999. The association of Clostridium botulinum type C with equine grass sickness: a toxicoinfection? *Equine Vet J* 31:492–9.
78. Hunter LC, Poxton IR. 2001. Systemic antibodies to Clostridium botulinum type C: do they protect horses from grass sickness (dysautonomia)? *Equine Vet J* 33:547–53.
79. McCarthy HE, French NP, Edwards GB, *et al*. 2004. Equine grass sickness is associated with low antibody levels to Clostridium botulinum: a matched case-control study. *Equine Vet J* 36:123–9.
80. Pirie RS. 2006. Grass sickness. *Clin Tech Equine Pract* 5:30–7.
81. Gilmour JS. 1973. Experimental reproduction of the neurological lesions associated with grass sickness. *Vet Rec* 92:565–6.
82. Gilmour JS, Mould DL. 1977. Experimental studies of neurotoxic activity in blood fractions

from acute cases of grass sickness. *Res Vet Sci* 22:1–4.
83. Cottrell DF, McGorum BC, Pearson GT. 1999. The neurology and enterology of equine grass sickness: a review of basic mechanisms. *Neurogastroenterol Motil* 11:79–92.
84. Gilmour JS, Brown R, Johnson P. 1981. A negative serological relationship between cases of grass sickness in Scotland and *Clostridium perfringens* type A enterotoxin. *Equine Vet J* 13:56–8.
85. McGorum BC, Wilson R, Pirie RS, *et al*. 2003. Systemic concentrations of antioxidants and biomarkers of macromolecular oxidative damage in horses with grass sickness. *Equine Vet J* 35:121–6.
86. Hahn CN, Mayhew IG, De Lahunta A. 2001. Central neuropathology of equine grass sickness. *Acta Neuropathol (Berl)* 102:153–9.
87. Johnson P, Dawson AM, Mould DL. 1983. Serum protein changes in grass sickness. *Res Vet Sci* 35:165–70.
88. Doxey DL, Milne EM, Gilmour JS, *et al*. 1991. Clinical and biochemical features of grass sickness (equine dysautonomia). *Equine Vet J* 23:360–4.
89. Wales AD, Whitwell KE. 2006. Potential role of multiple rectal biopsies in the diagnosis of equine grass sickness. *Vet Rec* 158:372–7.
90. Greet TR, Whitwell KE. 1986. Barium swallow as an aid to the diagnosis of grass sickness. *Equine Vet J* 18:294–7.
91. Wijnberg ID, Back W, de Jong M, *et al*. 2004. The role of electromyography in clinical diagnosis of neuromuscular locomotor problems in the horse. *Equine Vet J* 36:718–22.
92. Wijnberg ID, Franssen H, Jansen GH, *et al*. 2006. The role of quantitative electromyography (EMG) in horses suspected of acute and chronic grass sickness. *Equine Vet J* 38:230–7.
93. Hahn CN, Mayhew IG. 2000. Phenylephrine eyedrops as a diagnostic test in equine grass sickness. *Vet Rec* 147: 603–6.
94. Milne E. 2005. The equine grass sickness fund: management of chronic grass sickness. Retrieved on Oct 10, 2006, from http://www.grasssickness.org.uk.
95. Pirie RS. 2005. Equine grass sickness fund: potential management practices which may reduce the risk of grass sickness. Retrieved on Oct 10, 2006, from http://www.grasssickness.org.uk.
96. Doxey DL, Pogson DM, Milne EM, *et al*. 1992. Clinical equine dysautonomia and autonomic neuron damage. *Res Vet Sci* 53:106–9.
97. Doxey DL, Milne EM, Woodman MP, *et al*. 1995. Small intestine and small colon neuropathy in equine dysautonomia (grass sickness). *Vet Res Commun* 19:529–43.
98. Gilmour JS. 1973. Observations on neuronal changes in grass sickness of horses. *Res Vet Sci* 15:197–200.
99. Gilmour JS. 1975. Chromatolysis and axonal dystrophy in the autonomic nervous system in grass sickness of equidae. *Neuropath appl Neurobiol* 1:39–47.
100. DeBowes RM, Leipold HW, Turner-Beatty M. 1987. Cerebellar abiotrophy. *Vet Clin North Am Equine Pract* 3:345–52.
101. Palmer AC, Blakemore WF, Cook WR, *et al*. 1973. Cerebellar hypoplasia and degeneration in the young Arab horse: clinical and neuropathological features. *Vet Rec* 93:62–6.
102. Fox J, Duncan R, Friday P, *et al*. 2000. Cerebello-olivary and lateral (accessory) cuneate degeneration in a juvenile American Miniature Horse. *Vet Pathol* 37: 271–4.
103. Hartley WJ, Kuberski T, LeGonidec G, *et al*. 1982. The pathology of Gomen disease: a cerebellar disorder of horses in New Caledonia. *Vet Pathol* 19:399–405.
104. LeGonidec G, Kuberski T, Daynes P, *et al*. 1981. A neurologic disease of horses in New Caledonia. *Aust Vet J* 57:194–5.
105. Kirkpatrick JG, Burrows GE. 1990. Locoism in horses. *Vet Hum Toxicol* 32:168–9.
106. Huxtable CR, Dorling PR. 1982. Poisoning of livestock by *Swainsona* spp.: current status. *Aust Vet J* 59:50–3.
107. Loretti AP, Colodel EM, Gimeno EJ, *et al*. 2003. Lysosomal storage disease in *Sida carpinifolia* toxicosis: an induced mannosidosis in horses. *Equine Vet J* 35:434–8.
108. De Lahunta A. 1990. Abiotrophy in domestic animals: a review. *Can J Vet Res* 54:65–76.
109. Baird JD, Mackenzie CD. 1974. Cerebellar hypoplasia and degeneration in part-Arab horses. *Aust Vet J* 50: 25–8.
110. Blanco A, Moyano R, Vivo J, *et al*. 2006. Purkinje cell apoptosis in Arabian horses with cerebellar abiotrophy. *J Vet Med A Physiol Pathol Clin Med* 53: 286–7.
111. Sponseller ML.1967. Equine cerebellar hypoplasia and degeneration. *Proc Annual Meeting Am Assoc Equine Pract* 13:123–6.
112. Turner Beatty M, Leipold HW, Cash W, *et al*. 1985. Cerebellar disease in the horse. *Proc Annual Meeting Am Assoc Equine Pract* 21:241–5.
113. Peneda C. 2006. Cerebellar abiotrophy. Retrieved on Nov 1, 2006, from http://www.vgl.ucdavis.edu/research/equine/CA.html
114. Dungworth DL, Fowler ME. 1966. Cerebellar hypoplasia and degeneration in a foal. *Cornell Vet* 56:17–24.

20
Equine Hepatic Encephalopathy

Samuel Hurcombe

Hepatic encephalopathy (HE) is a clinical neuropsychotic condition characterized by abnormal cerebral mental status in conjunction with severe hepatic insufficiency. It is a complex syndrome that has a multitude of manifestations that are usually referable to augmentation of neuronal inhibition and can potentially affect all ages and breed of horses. Advanced, decompensated hepatic disease from any number of primary or secondary causes can result in the development of HE. Acute, subacute, or chronic hepatocellular disease processes ultimately lead to an inability or inefficiency of the liver to metabolize and detoxify potential neurotoxins, of either endogenous or exogenous origin.

HE is considered to be a potentially reversible metabolic encephalopathy; however the target organ derangement (i.e., the neurons of the cerebrum) may be irreversible.[1,2]

HE is clinically recognized by alterations in motor symptoms, cognitive deficits as well as changes in the level of alertness potentially progressing to hepatic coma. Pathological features that have been identified include processes affecting glial cell and neuronal function, hyperammonemia, changes in the concentration of excitatory and inhibitory neurotransmitter systems, as well as osmotic changes with consequential cell swelling.[3]

The frequently documented liver diseases in the horse are acute hepatic necrosis,[4] chronic active hepatitis[4] caused by pyrrolizidine alkaloids, cholelithiasis,[5] and hemachromatosis.[4]

In foals, a toxic hepatopathy causing HE has been described following the oral administration of a viable *Aspergillus* sp. and iron supplement. The neuropathologic findings were consistent with changes observed in human adults with HE. Alzheimer's type II astrocytosis was observed in the cerebral white matter.[6]

End stage alimentary lymphoma with hepatic involvement has also been described as a cause for HE in the horse.[7] Inherited metabolic disease leading to HE has been reported in foals,[8] and congenital portal vein anomolies have been associated with HE.[9] Hepatic lipidosis, cirrhosis, and neoplasia can also result in HE.[10] The frequency of the development of HE by primary liver diagnosis varies; 9 out of 9 horses with cirrhosis developed HE, while 4/18 horses with acute hepatic necrosis, 2/8 with hepatic lipidosis and 1/5 with hepatic neoplasia developed clinical signs of HE.[10] A syndrome of idiopathic hyperammonemia with HE has been described as well.[11–13]

The treatment is frustrating and often times unrewarding. Despite the best efforts to reverse the clinical signs and pathologic development, continued progression often ensues.

CLINICAL SIGNS AND LABORATORY FINDINGS

There are no specific features of HE that are pathognomonic for the clinical presentation and that are distinguishable to other causes of cerebral dysfunction. A clinical staging classification for humans, according to the severity of cognitive deficits, has been developed.[14] This classification system has been adapted for the horse.[1] Table 20.1 is a summary of the clinical neurological observations at different stages of disease. The earliest phase of HE (stage 1) can be very subtle and easily missed by owners and veterinarians owing to only mild, bilaterally symmetrical forebrain impairment of intellect and behavior.

Table 20.1. Clinical Staging of HE According to Neurologic Observations

Stage	Clinical Observations
1	Subtle forebrain disturbances often dismissed as unusual behavior for the animal. Often missed
2	Episodic drowsiness, irritability, disorientation, constant pacing and/or circling. Head pressing may also be observed
3	Inappropriate responses to stimuli, stupor, aggression, fear, somnolence, depression, yawning, ptyalism
4	Recumbency, loss of motor control, periodic unconsciousness, coma. Seizures are infrequently observed

Adapted from Barton, 2004.[1]

As forebrain function becomes more affected, motor function, intellectual abilities, and consciousness become impaired. During stage 2, waxing and waning signs may be observed including drowsiness, irritability, depression, head-pressing (Figure 20.1), disorientation with aimless wandering and inappropriate behavior. Horses are obviously affected. In stage 3, somnolence develops and is characterized by an abnormal response to stimuli which can be either depressed or exaggerated. Often horses develop aggression and violent behavior, which is episodic in nature with periods of stupor in between. Aimless wandering, head pressing, ataxia, blindness, and circling can be seen. The final stage (stage 4) observed is when the horse becomes recumbent, loses motor control, lapses in and out of consciousness, and ultimately becomes comatose and/or dies.[1] Seizures are occasionally observed in the terminal stages of HE. Laryngeal/pharyngeal paralysis has been described in horses and ponies with pyrrolizidine alkaloid toxicosis, where this may represent a rare manifestation of neurologic disease.[15,16]

In addition to the neurological manifestations, other clinical signs may reflect liver failure such as photosensitization, jaundice, peripheral edema,[17] and ptyalism.[18]

Anecdotally, horses with HE exhibit an increased frequency of yawning; however, there is no acceptable theory to verify the mechanism of this phenomenon.

CAUSES AND PATHOPHYSIOLOGY

The definition stipulates that regardless of the specific etiology, the end result is cerebral dysfunction as a consequence of hepatic insufficiency. No published studies have shown an association between normal neuron and astrocyte function with normal hepatic parenchymal integrity, therefore the exact cause is still unclear.

In humans, a reduced level of awareness can be attributed to a significantly slowed and synchronized spontaneous brain oscillatory activity. Mini-asterixis is a term used to describe HE motor



Figure 20.1. Head pressing behavior in an encephalopathic Quarterhorse.

postural tremors and have recently been associated with thalamocortical and corticomuscular synchronization.[3] This phenomenon may be evident in horses as adoption of an abnormal stance and being unaware of surrounding activity.

There are a number of proposed *hypotheses* on the pathogenesis of HE, each with their own merit and potential pitfalls.[1,18] This probably strengthens the notion that HE has a multifactorial cause. Regardless, the pathophysiology of HE remains controversial and undefined. Any or all of the suggested mechanisms may truly be involved (Table 20.2).

Toxic Metabolite Theory

Probably the most widely known, published, and believed hypothesis is that pertaining to excessive accumulation of toxic metabolites in the blood associated with nitrogenous substrates in the gastrointestinal tract, which bypass the hepatocytes through functional or anatomical shunts. Dysfunction may be related to nitrogenous metabolite accumulation due to abnormalities of hepatocyte function or anomalies of portal-systemic vasculature (i.e., portocaval and portoazygous shunts).[19]

There is one case report describing an arteriovenous anomaly and portal vein thrombosis in a yearling Thoroughbred gelding that had periodic episodes of diffuse central nervous system (CNS) disease. The gelding was diagnosed with HE based upon history, clinical presentation, prolonged hepatic clearance of sulfobromophthalein (BSP), and increased plasma ammonia concentration. Characteristic histological findings were observed in brain sections.[19]

Many articles in the human literature describe the pathological lesions as being low grade chronic glial edema with subsequent alterations of glioneuronal communication. Other theories support a role of a N-methyl-D-aspartate (NMDA) receptor activation and oxidative stress in the pathogenesis of HE.[20,21] Haussinger and Schliess (2005) discuss a close interrelationship between astrocyte swelling, NMDA receptor signaling, glutamate accumulation, oxidative stress, and nitric oxide levels, with the end conclusion being they may all have a critical role in the pathogenesis and result in mutual amplification of neurologic disturbance.[20]

Precipitating factors for HE in humans have been identified and include ammonia accumulation, benzodiazepines (BZ), inflammatory cytokines, and hyponatremia all contributing to the severity of astrocyte pathology.[20] Similar risk factors have not been ascertained for the horse. Certain metabolites can have a direct or indirect effect on CNS function. Zinc is an important cofactor required in the urea cycle, and deficiency has been recently implicated in the pathogenesis of HE in humans. Another pathogenetic mechanism has been suggested where an accumulation of manganese into the basal ganglia contributes to the clinical manifestation of cognitive dysfunction.[22]

Swapna et al. (2006) demonstrated that in rats, given a potent hepatotoxin (thioacetamide), myelin phospholipid, cholesterol, sphingomyelin, phosphatidylserine and phosphatidylethanolamine were significantly decreased. The suggestion is that these changes were observed as a consequence of neuronal oxidative damage. Transmission electron microscopy showed considerable myelin membrane disruption. The consequences of myelin disruption may have a crucial role in the various psychomotor abnormalities (mini-asterixis), observed particularly in later stage HE.[23] These compounds are not assayed on a routine basis in the horse.

Hyperammonemia Theory

Ammonia is a product of the degradation of amino acids, amines, and purines. Ammonia is produced by enteric bacteria in the gut lumen, absorbed, and transported via the portal circulation to the liver. With advanced hepatic dysfunction, the conversion of ammonia to urea does not occur, and

Table 20.2. Theorized Mechanisms for the Development of Hepatic Encephalopathy

Gastrointestinal derived neurotoxins and hepatic insufficiency to detoxify
False neurotransmitter accumulation following plasmaamino acid imbalance (competitive inhibition)
Augmented activity of GABA in the CNS
Increased permeability of the blood–brain barrier
Impaired CNS energy metabolism

hyperammonemia results. Ammonia has a deleterious effect on cell membranes of neurons causing inhibition of Na-K-ATPase activity leading to a depletion of adenosine triphosphate (ATP).[24] Hyperammonemia has also been shown to decrease α-ketoglutarate formation in the Krebs cycle and subsequent synthesis of glutamine and ATP.[25]

Histological evidence of cerebral edema and astrocyte swelling at necropsy can be observed in cases of hyperammonemia associated encephalopathy of horses.[12] This results from the detoxification of ammonia to glutamate and glutamine by astrocytes. Glutamine synthase is an alternative pathway for ammonia detoxification, and in patients with liver failure, glutamine accumulates. Tissue associated phosphate-activated glutaminase (PAG) deaminates glutamine to glutamate and ammonia. PAG activity has been shown to be increased in cirrhotic patients with mild HE.[26] In the brain, PAG localized in astrocytes produces ammonia and free radicals from the metabolism of glutamine. Experimentally, the blockade of PAG with 6-oxo-5-norleucine will reduce the CNS effects of hyperglutaminemia and hyperammonemia.[26]

Several studies have shown an increase in glutamine concentration using magnetic resonance spectroscopy (MRS) in human patients with HE. This increased glutamine concentration also correlated with an increased ammonia concentration following an oral glutamine challenge test as well as impaired attention tests in one study, suggesting a critical role of glutamine and ammonia in the causation of clinical signs.[27]

The marked depression and somnolence so often seen in cases of HE may be attributed to a down regulation of glutamate receptors. Glutamate is a major excitatory neurotransmitter on the mammalian brain; however, when there are fewer glutamate binding sites for stimulation, there may be a tendency for inhibitory neuronal activity to override the paradoxical elevation in astrocytic glutamate production.

Hyperammonemia also generates the production of nitric oxide that may lead to the subsequent production and accumulation of peroxides and reactive oxygen species (ROS). These supercharged small molecules can induce oxidative neuronal cell membrane damage contributing to the development of encephalopathy.[1]

Furthermore, in support of the hyperammonemia hypothesis is the observation of human children with a congenital enzyme deficiency that also have elevated ammonia concentrations and encephalopathy. Therapeutic trials aimed at reducing ammonia production and absorption do ameliorate the clinical signs referable to encephalopathy in these patients.[22,28]

Conversely, however, there appears to be a poor correlation between detectable serum ammonia concentrations and the severity of clinical signs observed in equine patients with HE.[16] Furthermore, when ammonia is administered, the electroencephalographic (EEG) findings are not consistent with the encephalopathy associated with liver disease.[21]

It appears that ammonia may certainly have a critical role in the pathogenesis and clinical presentation of HE but is unlikely to be the sole cause of the encephalopathic signs observed in clinical patients.

Experimentally, hypoosmotic swelling triggers a rapid oxidative stress response involving the action of NADPH oxidase isoenzymes, followed by tyrosine nitration of specific distinct astrocytic proteins. These changes were also observed in astrocytes exposed to ammonia, inflammatory cytokines (TNF-α, IFN) and BZs. NMDA receptor activation was an upstream consequence of protein tyrosine nitration (PTN).[1,21] Perivascular cerebral astrocytes appear to be particularly susceptible to PTN impacting on blood–brain barrier permeability, facilitating the passage of gastroenterically produced nitrogenous metabolites. PTN causes inactivation of glutamine synthase perpetuating ammonia accumulation.[21]

Synergistic Neurotoxin Theory

A more complex and integrative hypothesis than simple hyperammonemia has been proposed for the pathogenesis of HE. The synergistic neurotoxin hypothesis implicates ammonia in addition to a series of other gut-derived molecules including mercaptans, short-chain fatty acids (SCFA) and phenols. An accumulation of these molecules may induce cerebral dysfunction through augmentation of and interaction with endogenous toxic metabolic abnormalities, hence the synergistic effect. When elevated alone, each of these substances is unlikely to affect the CNS. A consistent flaw in most HE theories is observed again, where serum mercaptan concentration correlates poorly with the severity of HE clinical signs.[1,29]

Competitive Inhibition (The False Neurotransmitter) Theory

In advanced liver failure, the concentration of "true" neurotransmitters such as dopamine (DA) and norepinephrine (NE) becomes depleted and the concentration of "false" neurotransmitters such as octapamine and phenylethanolamine increases.[1,18] The resultant effect is reduced neuronal excitation and increased neuronal inhibition.[1] An increased serum concentration of aromatic amino acids (AAA) and concurrent decrease in serum concentrations of branched chain amino acids (BCAA) is observed in patients with liver failure.[30] This occurs as a result of increased skeletal muscle catabolism associated with an elevated serum glucagon concentration observed in patients with hepatic disease.[31] The catabolic products of muscle breakdown include AAA and BCAA: however, with compromised hepatic metabolic function, the metabolism of AAA is reduced, whereas BCAA are also metabolized in muscle and adipose tissues. The net result is an elevation in serum AAA concentration. The normal BCAA:AAA ratio in the horse is 3.5 to 4.5. The risk of HE is considered low, medium, or high with corresponding values of 3.0 to 3.5, 2.5 to 3.0, or less than 2.5, respectively.[32] Table 20.3 lists some amino acids and their chemical configuration groupings.

The result of an increased AAA:BCAA ratio and increased CNS glutamine concentration (presumably via concurrent ammonia retention) promotes the influx of AAA into the CNS and efflux of glutamine from the CNS through an exchange apparatus within the blood–brain barrier. Phenylalanine competes with tyrosine for tyrosine hydroxylase causing a decreased DA concentration. Excessive uncatalysed tyrosine can be converted to tyramine (by decarboxylation) and further modified to form octapamine, a false neurotransmitter.[33] Elevated tyrosine concentrations may also competitively compete for dopamine β-oxidase and reduce the production of NE. Another false neurohormone is phenylethanolamine, a product of phenylalanine metabolism.

Tryptophan is converted to 5-hydroxytryptophan (5-HT; serotonin) and oxindole. These are powerful neuroinhibitors and exhibit a potent sedative effect.[24] Horses with evidence of HE and hepatic changes associated with pyrrolizidine alkaloid toxicity exhibit an altered AAA:BCAA in favor of AAA predominance, and when treated with BCAA-rich solutions, a reduction in the severity of neurological signs was observed.[34]

Supportive to this theory is the observation of elevated cerebrospinal fluid (CSF) concentrations of octopamine, serotonin, and phenylalanine with concurrent elevations in serum concentrations in patients with HE.[1]

In controlled clinical trials of humans, however, altering the AAA:BCAA ratios to favor BCAA abundance did not improve the clinical signs of HE. There is a poor correlation in human patients between a high AAA:BCAA ratio and clinical signs of HE. Similarly, octopamine elevations alone have not been demonstrated to cause HE.

Table 20.3. Amino Acid Groups

Aromatic Amino Acids (AAA)	Branched Chain Amino Acids (BCAA)
Phenylalanine	Valine
Tyrosine	Isoleucine
Tryptophan	Leucine

Inhibitory Neurotransmitter Theory

Augmentation of the neurotransmitters γ-aminobutyric acid (GABA), endogenous benzodiazepines (eBZ), and serotonin in conjunction with a depression of the glutamine neuroexcitatory system have been proposed as a theory for the cerebral dysfunction associated with HE.

GABA is released from presynaptic neurons, where it binds to specific GABA receptor sites on an adjacent postsynaptic nerve membrane. The result of this interaction is to promote the opening of chloride ion channels and conductance of ionic chloride causing membrane hyperpolarization and ultimately the inhibition of the postsynaptic potential. The liver is responsible for up to 80% of GABA metabolized in the normal horse; hence, liver disease can be expected to have an effect upon GABA metabolism and accumulation.[1]

Ammonia has been shown to act synergistically with eBZ and may contribute to GABA-induced neuronal inhibition observed with BZ receptor stimulation. In an in vitro animal model of HE, results supported the hypothesis that there is an increased functional GABAergic tone that is mediated allosterically through a BZ receptor via a diazepam like substance (eBZ).

Although the concept of increased GABAergic tone is a key to the pathogenesis of HE, conflicting results as to the role of endogenous BZ receptor ligand continue to confuse and cloud the true mechanism of action.[35] Clinical trials using BZ antagonists such as flumazenil have resulted in improved consciousness and reduced EEG changes associated with HE in humans.[36] Similar studies in the horse are not available.

DIAGNOSIS

There are no pathognomonic diagnostic findings for HE. The diagnosis of HE can be based upon historical information, physical examination, clinicopathological aberrations associated with hepatic insufficiency or disease, and exclusion of other causes of cerebral dysfunction. Diagnosis is supported primarily by the presence of clinical signs associated with biochemical or pathologic evidence of liver disease.

Historical factors that may be important in the evaluation of horses with suspected HE include a history of recent equine origin biologicals, pyrollizidine alkaloid plant ingestion, weight loss or icterus, exposure to potentially toxic pharmaceuticals or herbal medications, or previous signs of liver disease.

Physical examination findings may vary according to the stage of HE development, and at times, the horse can be too manic or aggressive to examine safely. Depression, lack of coordination, and altered behavior (i.e., aimless wandering) are often the first noticeable signs that alert the clinician. Other clinical signs include ataxia, stumbling, muscle weakness, head pressing, circling, or blindness. All clinical signs are referable to diffuse encephalopathic disease.

Table 20.4 is a list of differential diagnoses for a horse that presents for possible encephalopathy. Additional rule-outs are discussed in Section 2, Chapter 6.

Clinicopathological Testing

A complete blood count (CBC) and serum fibrinogen concentration may reflect an infectious/inflammatory lesion. A normal CBC is often found in HE. However erythrocytosis and/or an inflammatory leukogram may be present with significant liver disease.[37] Serum biochemistry assay including electrolyte and glucose concentrations, serum enzyme activities, albumin, triglycerides, and bilirubin (total, conjugated, and unconjugated) concentrations, coagulation profiles, blood ammonia, and serum bile acids may help support a diagnosis of hepatic disease or another differential. Blood urea nitrogen (BUN) assay may reveal a low (subnormal) result associated with altered ammonia metabolism. Serum immunoglobulin titers may be appropriate testing for viral encephalitides and assay for toxicological agents in light of other clinical findings.

Table 20.4. Differential Diagnoses for the Encephalopathic Horse. Additional Considerations Discussed in Section 2, Chapter 6

Head trauma
Viral encephalitis (including WNV, EEE, WEE, VEE, Rabies virus)
Equine protozoal myeloencephalitis (EPM)
Intracranial abscess (including *Streptococcus, Rhodococcus, Listeria*)
Leukoencephalomalacia (moldy corn toxicosis)
Verminous encephalitis (e.g., *Halicephalobus* spp.)
Organophosphate toxicity
Nigropallidal encephalomalacia (yellow star thistle toxicosis)
Botulism
Heavy metal toxicosis (arsenic, lead)
Intracranial neoplasia (cholesterol granuloma etc.)
Adverse drug reactions (e.g., fluphenazine)
Meningitis

WNV: West Nile virus; EEE: Eastern equine encephalitis; WEE: Western equine encephalitis; VEE: Venezuelan equine encephalitis

Blood ammonia is relatively unstable, and the sample should be collected into a tube with heparin as an anticoagulant and either assayed or frozen immediately. Interpretation of the results is often difficult due to the effects of ammonia-generating and urea-utilizing bacteria in the gut. Also, the timing of the blood collection in relation to the clinical event (if intermittent) may make interpretation challenging. Normal values for blood ammonia in the horse vary according to diet and between labs but have been reported in the range of 13 to 108 μg/dL (7.6–63.2 μmol/L).[38] Due to the observed volatility in blood ammonia concentrations, it may be worthwhile to take several samples over a 1 to 2 day period.

In one review, 18 horses presented for HE had hyperammonemia with plasma ammonia concentrations greater than 90 μmol/L. The severity of clinical signs was not proportional to the degree of plasma ammonia concentration, however. Over 50% had hyperglycemia, none were hypoglycemic, and none had abnormally low serum urea concentrations. All had elevations in gamma-glutamyl transferase

(GGT) activity, glutamate dehydrogenase (GDH) activity, and serum bile acids.[16]

In another study of horses with HE, blood ammonia concentrations were routinely found to be higher in horses with HE compared to normal controls, but a wide range in values was found, as well as abrupt decreases in concentration even within the same day. Serum urea values and glucose concentration were much less frequently abnormal than blood ammonia.[10] In another report of 2 foals with an inherited metabolic disorder which results in hyperammonemia, blood ammonia concentrations ranged from 273 to 503 μg/dl associated with clinical signs of encephalopathy (dementia, ataxia, circling, teach grinding). Clinical signs abated, associated with a decrease in ammonia concentration.[8] Figure 20.2 is a suggested algorithm for the diagnostic work-up of liver disease.

Several other biochemical markers have been evaluated and found to be abnormal in human patients with HE. Leptin, a hormone thought to interact in lipid metabolism, was increased in encephalopathic patients. Conversely, transferrin and insulin-like growth factor-1 (IGF-1) were decreased in some patients.[39] The relevance of these variables is unknown at this stage but the condition may be due to insulin insensitivity observed in chronic liver disease.[31]

A lumbosacral CSF tap should be attempted if safe to do so. This will assist in ruling in or out a number of other potential causes of abnormal mentation and CNS disease. Horses with HE have a normal CSF cytology and protein concentration; however, a second concurrent disease may confuse these results. Computed tomography (CT) scanning of the head may show brain edema, but this alone is not confirmatory for HE.

Electrodiagnostic Testing

In human patients with HE, EEG changes include a symmetrical generalized retardation of cerebral activity. However, while being quite a sensitive marker for the condition, other disease states including metabolic encephalopathies (e.g. hyponatremia, hypoglycemia) also exhibit similar abnormalities. EEG changes in HE show triphasic waves; however, this is also observed in patients with encephalopathy due to severe uremia.[40] Specific changes in the

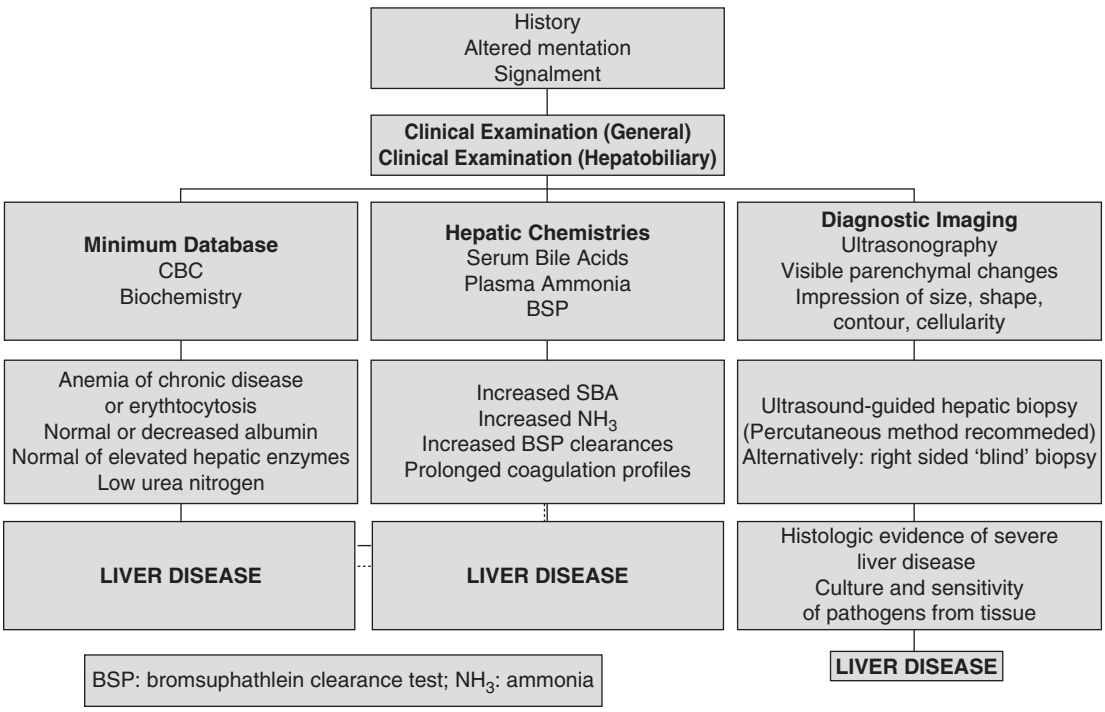


Figure 20.2. Algorithm for the diagnosing liver disease in the horse.

equine EEG with HE have not been reported. However, principles of EEG changes observed in HE and some other metabolic encephalopathies include:

1. varied degrees of wave slowing
2. assorted mixtures of epileptic discharge
3. high incidence of triphasic waves, and
4. reversibiliy of EEG findings after appropriate therapy[40]

Utilizing visual evoked potentials (VEP) has a greater specificity than conventional EEG.

VEP reflect the pattern and magnitude of postsynaptic neuronal activity evoked by a visual afferent stimulus.

There is a distinctively characteristic VEP response pattern seen in humans with HE; however, the lack of ease in performing this in the horse prohibits the use of this tool from being available. Brainstem auditory-evoked potentials may be a practical alternative.

Anatomic Pathology and Histopathology

There are no characteristic gross or microscopic findings observed in the cerebral tissues of horses with HE. Astrocytosis and astrocyte swelling (Alzheimer's type 2 cells) in addition to cerebral edema may be present. Astrocyte accumulation of glutamine leads to neuronal swelling and edema.

Histopathological changes characteristic of emperipolesis have been identified in the white matter of the cerebral cortex. Emperipolesis is the process whereby hypertrophic astrocytes engulf one to several oligodendrocytes, which can lead to the destruction of myelin and inflammation of the white matter. It is not a pathognomonic finding of HE because it is also observed in multiple sclerosis, cerebral infarction, and Creutzfeldt-Jakob prion disease in people.[41] Diffuse cerebral edema (either grossly or microscopically) has not been reported to be a significant finding in horses with HE.

The presence of gross and microscopic abnormalities of the liver are important findings in support of the diagnosis. In cases of idiopathic hyperammonemia or uremic encephalopathy, the liver will be normal.

THERAPEUTIC MANAGEMENT

Management of HE is somewhat controversial and poorly defined. While some clinicians have tried traditional therapies with minimal efficacy, others vehemently advocate therapy aimed at reducing intestinal absorption of ammonia. Regardless of the clinician preference, therapy should be aimed at alleviating the cause of hepatic dysfunction (where possible), dietary protein restriction, and supportive/palliative care.

For maniacal behavior, heavy sedation is required. Xylazine (0.25–1 mg/kg IV or IM) is a good choice to control the animal before other therapy is instituted. Avoid BZ tranquilizers such as diazepam, as this may potentiate the GABAergic system.

Most drugs are normally metabolized by the hepatocytes and unique cytochrome P450 metabolizing enzyme systems. However, given the concurrent severe hepatic disease, judicious use of pharmacological therapies should be exercised, as the potential for overdosing is increased.

Flumazenil (a BZ antagonist) has been used in human medicine to temporarily lessen and somewhat ameliorate the signs of HE. The overall success of flumazenil in both humans and dogs with HE associated with portosystemic shunts is low, and in horses has been rarely tried. It has a relatively short half-life (~1 h) and can potentially induce seizure activity.

Flumazenil has been shown to have only a transient beneficial effect in a subpopulation of HE patients in numerous controlled clinical trials.[36] A new BZ antagonist, Sarmazenil, has shown promise in treating humans patients with HE. Nonbenzodiazepine GABA receptor complex modulators are being identified and are thought to play a vital role in the pathogenesis of encephalopathic disease and may provide a new mechanistic basis of therapy in the future.[36] Published clinical trials in veterinary medicine are lacking at this time.

Lowering Serum Ammonia Concentrations

Therapeutic options aimed at lowering plasma ammonia concentration include drugs that alter the number of ammonia-producing enteric bacteria and colonic pH.

Antibiotics

Antibiotics given orally that are effective at altering colon bacterial populations include neomycin and metronidazole. Metronidazole is a less preferred option given its extensive hepatic metabolism and potential for toxicity characterized by anorexia. Neomycin, although effective, can cause mucosal

irritation with prolonged usage and cause severe acute diarrhea.

Rifaximin is a synthetic oral antibiotic, similar in structure to rifamycin antibiotics (i.e., rifampicin) and has now been used extensively in human patients. In humans, it has remarkable safety and efficacy and has the highest benefit-risk ratio of all treatments for HE. It displays a wide spectrum of antibacterial activity for Gram-negative and Gram-positive aerobes and anerobes.[2] Rifaximin has a very low level of systemic absorption, and this property might cause serious enterocolitis, precluding its use in horses. No published clinical trials in horses have been conducted and specific recommendations for its use cannot be made at this time.

In cases of hyperammonemic HE associated with severe periportal and bridging fibrotic hepatopathy, serial monitoring of serum GGT activity is recommended as an objective marker of response to therapy. In one paper, the recommendation to continue therapy until serum GGT concentrations normalize was suggested.[5] The median treatment time was 51 days (range 17 to 124 days) with antibiotics. Table 20.5 gives suggested doses for drugs used in the symptomatic treatment of HE in the horse.

Lactulose

Lactulose is a dissacharide molecule that avoids enzymatic cleavage by mammalian small intestine brush border enzymes, reaching the colon unchanged. It is metabolized by resident bacteria to SCFA, namely, lactate, formate, and acetate as well as carbon dioxide. These SCFA acidify the colonic luminal contents and lower the colon pH. This lowered pH favors the ionization of the highly soluble and uncharged ammonia molecule to form a more polar, relatively insoluble ammonium ion. This results in less ammonia absorption into the portal circulation and enhanced ammonium ion excretion in feces. The second effect of increasing the SCFA colonic content is that of creating an increased osmotic gradient. A net retention and influx of water increases the colonic total water content producing a laxative effect and increasing the loss of ammonia during defecation. Interestingly, in one study on healthy ponies, there was no significant reduction in the plasma ammonia concentration following the administration of oral lactulose.[42] The effects of lactulose in horses with elevated blood ammonia concentrations has not been reported.

Table 20.5. Suggested Drug Dosages for HE Therapeutics

Drug	Dose
Metronidazole	15–25 mg/kg PO TID
Neomycin	10–50 mg/kg PO BID-QID for 2 days
Sodium ampicillin	10 mg/kg IV/IM QID
Potassium penicillin	22,000 IU/kg IV QID
Gentamicin sulfate	6.6 mg/kg IV SID
Lactulose	0.3–0.5 ml/kg PO QID
Omeprazole	4 mg/kg PO SID
Ranitidine	6.6 mg/kg IV/PO TID
Cimetidine	6.6–10 mg/kg IV TID
L-Carnitine	25–50 mg/kg PO SID
Mineral oil	10–16 ml/kg PO SID
Sodium sulfate	1 g/kg PO SID for 3 days

Ancillary Therapies

Biochemical characteristics of liver disease include a low concentration of circulating BCAA, elevated AAA, and elevations in methionine. In 2 large randomized controlled trials of humans, BCAA supplementation appeared to be associated with a decrease in frequency of HE complications and improved the nutritional status of the patient.[30]

In addition, ornithine-aspartate administration has been suggested as a beneficial adjunct to therapy in humans.[43]

L-Carnitine and acetyl-L-carnitine (ALCAR) may prove to be appropriate adjunct therapies for the treatment of HE in horses.

In one study, the visual evoked potentials measured at 100 msec after pattern reversal latencies (P100) (prominent positive component) were significantly shorter in human hyperammonemic HE patients who were administered a single short intravenous infusion of ALCAR, suggesting that at least transient improvement in neuronal function can occur in these patients.[44]

Another study showed that L-carnitine may have an important protective effect in these hyperammonemic HE patients.[45]

Mineral oil or sodium sulfate can be administered via a nasogastric tube to facilitate fecal passage and reduce the absorption of ammonia. Supplemental zinc is recommended in deficient patients.

Reducing Cerebral Edema

Since the principal histological finding is astrocyte swelling, glial edema, and emperipolesis, the administration of mannitol and/or dimethylsulfoxide (DMSO) has been advocated, especially in severe cases. Mannitol has been used in human patients at a dose of 0.5 mL/kg body mass over a 10 min period.[46] While there is no evidence-based clinical trial using DMSO in cerebral edema models in the horse, this drug has been used extensively for the purposes of free radical scavenging, reducing edema, and inhibiting inflammation in the horse for a variety of conditions. A suggested dose rate is 0.5–1 g/kg IV as a 10–20% solution every 12–24 h for 1–3 days.

Dietary Management

Reducing the lipid and protein content of the diet will assist in reducing the requirement for metabolic processes carried out by the liver. Providing nourishment in the form of simple monosaccharide sugars such as glucose or dextrose can be done. Given that the liver has a vital role in carbohydrate metabolism, excessive administration may lead to a glycogen storage hepatopathy, exacerbating the degree of hepatic dysfunction.

Highly digestible feeds including good quality grass hay, oats, barley, cracked corn, and softened beet pulp are good sources of simple carbohydrates and have been shown to have an enriched ratio of BCAA.[47] In addition, polyionic isotonic balanced electrolyte fluids (oral or intravenous) supplemented with dextrose can be given in the immediate stage of therapy, as some of these horses do not drink. Normal saline (0.9% NaCl) is a good choice in preference to lactated Ringers solution which requires hepatic metabolism to convert lactate to bicarbonate. A 2.5–5% dextrose concentration solution can be added to the fluid therapy. Measuring serum glucose concentrations is recommended to monitor the glycemic status of the patient.

PROGNOSIS

In one retrospective study evaluating a large number of horses with liver disease, the most useful noninvasive prognostic indicator was the severity of clinical signs including stage of HE. Increased plasma fibrinogen concentrations and subnormal serum creatinine concentrations had a direct association with nonsurvival.[37] Prognosis can depend on the underlying hepatic disease. For instance, pyrrolizidine alkaloid toxicity carries a poor to guarded long-term prognosis, but most horses survive many years after the diagnosis is confirmed. Regardless of the cause, the prognosis is considered poor for horses with hepatic disease and neurologic dysfunction. Some reports have stipulated up to 40% of horses with HE survive beyond 6 months. Bearing this in mind, this certainly justifies attempted therapy on a short-term basis.

REFERENCES

1. Barton, MH. 2004. Disorders of the liver. In *Equine Internal Medicine*, edited by Reed SM, Bayley W, Sellon D, 958–62. St. Louis: Elsevier.
2. Festi D, Vestito A, Mazzella G, *et al*. 2006. Management of hepatic encephalopathy: focus on antibiotic therapy. *Digestion* 73 (Suppl. 1):94–101.
3. Timmermann L, Butz M, Gross J, *et al*. 2005. Neural synchronization in hepatic encephalopathy. *Metab Brain Dis* 20:337–46.
4. Olsman AF, Sloet van Oldruitenborgh-Oosterbaan MM. 2004. Primary liver disease in the horse. *Tijdschr Diergeneeskd* 129:510–22.
5. Peek SF, Divers TJ. 2000. Medical treatment of cholangiohepatitis and cholelithiasis in mature horses: 9 cases (1991–1998). *Equine Vet J* 32:301–6.
6. Acland HM, Mann PC, Robertson JL, *et al*. 1984. Toxic hepatopathy in neonatal foals. *Vet Pathol* 21:3–9.
7. Schnabel LV, Njaa BL, Gold JR, *et al*. 2006. Primary alimentary lymphoma with metastasis to the liver causing encephalopathy in a horse. *J Vet Intern Med* 20:204–6.
8. McConnico RS, Duckett WM, Wood PA. 1997. Persistent hyperammonemia in two related Morgan weanlings. *J Vet Intern Med* 11:265–66.
9. Beech, J. 1977. Portal vein anomaly and hepatic encephalopathy. *J Am Vet Med Assoc* 170:164–6.
10. West HJ. 1996. Clinical and pathological studies in horses with hepatic disease. *Equine Vet J* 28:146–56.
11. Peek SF, Divers TJ, Jackson CJ. 1997. Hyperammonaemia associated with encephalopathy and abdominal pain without evidence of liver disease in four mature horses. *Equine Vet J* 29:70–4.
12. Hasel KM, Summers BA, deLahunta, A. 1999. Encephalopathy with idiopathic hyperammonemia and Alzheimer type II astrocytes in Equidae. *Equine Vet J* 31:478–82.
13. Mair T, Jones RD. 1995. Acute encephalopathy and hyperammonemia in a horse without evidence of liver disease. *Vet Rec* 137:642–3.

14. Gammel SH, Jones EA. 1989. Hepatic encephalopathy. *Med Clin North Am* 73:793–813.
15. Pearson EG. 1991. Liver failure attributed to pyrrolzidine alkaloid toxicosis and associated inspiratory dyspnea in ponies: three cases (1982–1988). *J Am Vet Med Assoc* 198:1651–4.
16. McGorum BC, Murphy D, Love S, *et al*. 1999. Clinicopathological features of equine primary hepatic disease: a review of 50 cases. *Vet Rec* 145:134–9.
17. Zientara S, Trap D, Fontaine JJ, *et al*. 1994. Survey of equine hepatic encephalopathy in France in 1992. *Vet Rec* 134:18–19.
18. Lorenz MD, Kornegay JN. 2004. Systemic or multifocal signs. In *Handbook of Veterinary Neurology*, edited by Lorenz MD, Kornegay JN, 362–3. Philadelphia: Saunders.
19. Beech J, Dublielzig R, Bester R. 1977. Portal vein anomaly and hepatic encephalopathy in a horse. *J Am Vet Med Assoc* 170:164–6.
20. Haussinger D, Schliess, F. 2005. Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. *Neurochem Int* 47:64–70.
21. Haussinger D, Gorg B, Reinehr R, *et al*. 2005. Protein tyrosine nitration in hyperammonemia and hepatic encephalopathy. *Metab Brain Dis* 20: 285–94.
22. Mas A. 2006. Hepatic encephalopathy: from pathophysiology to treatment. *Digestion* 73 (Suppl. 1):86–93.
23. Swapna I, Kumar KV, Reddy PV, *et al*. 2006. Phospholipid and cholesterol alterations accompany structural disarray in myelin membranes of rats with hepatic encephalopathy induced thioacetamide. *Neurochem Int* 49:238–44.
24. Albrecht J, Jones E. 1999. Hepatic encephalopathy: molecular mechanisms underlying the clinical syndrome. *J Neurol Sci* 170:138.
25. Bessman SP, Bessman AN. 1975. The cerebral and peripheral uptake of ammonia in liver disease with a hypothesis for the mechanism of hepatic coma. *J Clin Invest* 34:622.
26. Romero-Gomez, M. 2005. Role of phosphate-activated glutaminase in the pathogenesis of hepatic encephalopathy. *Metab Brain Dis* 20: 319–25.
27. Minguez B, Garcia-Pagan JC, Bosch J, *et al*. 2006. Noncirrhotic portal vein thrombosis exhibits neuropsychological and MR changes consistent with minimal hepatic encephalopathy. *Hepatology* 43:707–14.
28. Loguerico C, Frederico A, De Girolamo V, *et al*. 2003. Cyclic treatment of chronic hepatic encephalopathy with rifaximin. Results of a double-blind control clinical study. *Minerva Gastroenterol Dietol* 49:53–62.
29. Jover R, Madaria E, Felipo V, *et al*. 2005. Animal models in the study of episodic hepatic encephalopathy in cirrhosis. *Metab Brain Dis* 20:399–408.
30. Charlton M. 2006. Branched-chain amino acid enriched supplements as therapy for liver disease. *J Nutrit* 136: 295–8.
31. Notle W, Hartmann H, Ramadon G. 1995. Glucose metabolism and liver cirrhosis. *Exp Clin Endocrinol Diabetes* 103:63–74.
32. Gulick BA, Rogers QR, Knight HD. 1978. Plasma amino acid profiles in horses with hepatic disease. *Proc 21st Annual Meet Am Assoc Eq Pract* 517.
33. Alexander WF, Spinder E, Harty RF, *et al*. 1989. The usefulness of branched chain fatty acids with acute or chronic hepatic encephalopathy. *Am J Gastroenterol* 84:91.
34. Mendel VE, Witt MR, Gitchell BS, *et al*. 1988. Pyrrolizidine alkaloid-induced liver disease in horses: an early diagnosis. *Am J Vet Res* 49: 572–8.
35. Iversen P, Hansen DA, Bender D, *et al*. 2006. Peripheral benzodiazepine receptors in the brain of cirrhosis patients with manifest hepatic encephalopathy. *Eur J Nucl Med Mol Imaging* 33: 810–6.
36. Ahboucha S, Butterworth RF. 2005. Role of endogenous benzodiazepine ligands and their GABA-A-associated receptors in hepatic encephalopathy. *Metab Brain Dis* 20:425–37.
37. Durham AE, Newton JR, Smith KC, *et al*. 2003. Retrospective analysis of historical, clinical, ultrasonographic, serum biochemical and haematological data in prognostic evaluation of equine liver disease. *Equine Vet J* 35:542–7.
38. Barton MH, Morris DD. 1998. Diseases of the Liver. In *Equine Internal Medicine*, edited by Reed SM, Bayley W, 707–38. Philadelphia: Saunders.
39. Kim HK, Oh HJ, Nam SW, *et al*. 2006. Clinical and biochemical parameters of nutrition to predict hepatic encephalopathy in cirrhotic patients. *Korean J Gastroenterol* 47:44–51.
40. Lin CC. 2005. EEG manifestations in metabolic encephalopathy. *Acta Neurol Taiwan* 14:151–61.
41. Nishie M, Mori F, Houzen H, *et al*. 2006. Oligodendrocytes within astrocytes (emperipolesis) in the cerebral white matter in hepatic and hypoglycemic encephalopathy. *Neuropathology* 26:62–5.
42. Scarratt WK, Warnick LD, 1989. Effects of oral administration of lactulose in healthy horses. *J Equine Vet Sci* 18:405.

43. Bruha R, Drastich P, Hulek P, *et al*. 2006. The diagnosis and therapy of hepatic encephalopathy. *Vnitr Lek* 52:85–6.
44. Siciliano M, Annicchiarico BE, Lucchese F, *et al*. 2006. Effects of a single, short intravenous dose of acetyl-L-carnitine on pattern-reversal visual evoked potentials in cirrhotic patients with hepatic encephalopathy. *Clin Exp Pharmacol Physiol* 33:76–80.
45. Malaguarnera M, Pistone G, Elvira R, *et al*. 2005. *World J Gastroenterol* 11:197–202.
46. Riordan S, Williams R. 1997. Treatment of hepatic encephalopathy. *N Eng J Med* 337:473.
47. Divers TJ. 1990. Therapy of liver failure. In *Large Animal Internal Medicine*, edited by Smith BP, 820–1. St. Louis: Mosby.

21
Electrolytes and Neurological Dysfunction in Horses

Samuel Hurcombe

The ability of horses to maintain electrolyte homeostasis is imperative for normal cellular function and well-being. Abnormalities of electrolyte concentration can manifest serious clinical signs if left unresolved. Normal intracellular and extracellular electrolyte concentrations are both important, particularly in excitable tissues such as nerves and muscles. These two systems are intimately interconnected and are dependent on one another for normal function. Little work has been performed directly in horses, hence much of the discussion is derived from evidence-based studies in human medicine. Where available, species-specific information is given.

SODIUM

Hyponatremia

Hyponatremia is defined as a serum sodium concentration below 134 mmol/L.[1–5] Hyponatremia causes edema of the brain due to excessive water entry. Due to the limits of the cranial vault, there is a subsequent increase in intracranial pressure that can potentially lead to additional neuropathological sequelae, including death.[1]

There is adaptation during hyponatremia where solutes (osmolytes) leave the brain within hours, with water following and reducing the degree of edema. However, the brain has only a limited capacity for adaptation. During subsequent sodium replenishment, the reestablishment of intracerebral osmolytes occurs, but their re-uptake is more delayed (±5 days). These mechanistic processes can be overwhelmed leading to severe brain damage.[1]

Both hypervolemic and hypovolemic hyponatremic states are reported in other species. Acute water intoxication can result from psychogenic polydipsia or following intravenous administration of hypotonic solutions.

Hypovolemic hyponatremic encephalopathy has been reported in a horse. One case report describes this phenomenon in a foal with diarrhea.[6] Profuse diarrhea results in hypovolemic states due to large fluid and electrolyte losses. With subsequent water ingestion (a hypotonic fluid), a rapid reduction in serum sodium concentration and serum osmolality may occur.

Other causes of hyponatremia in horses can occur secondary to renal failure, ruptured urinary bladder (especially foals), and iatrogenic water overload due to enteral and parenteral administration of hypotonic fluids.[7,8]

Foals with uroperitoneum are often hyponatremic. Mare's milk, the usual diet, is low in sodium and high in potassium concentration. When the urinary bladder ruptures and uroperitoneum develops, a large volume of a hyponatremic solution builds up in the abdomen, drawing sodium from the blood and lowering the serum Na^+ concentration.

Drug administration has been reported to be a cause of hyponatremia in addition to other electrolyte derangements. In one case report, a 9-year-old Quarter horse gelding developed iatrogenic hypoadrenocorticism (Addison's disease) following chronic administration of stanozolol.[9] Other reports from the human literature report a well-described syndrome of hyponatremia following the administration of carbamazepine, which may have implications in equine medicine as this drug is often used for the treatment of idiopathic head-shaking in horses.[10] The administration of desmopressin for the treatment

of hemostatic disorders in humans has been shown to cause dilutional hyponatremia through a reduction in the renal excretion of free water.[11] Similarly, the endocrinological syndrome of inappropriate antidiuretic hormone secretion' (SIADHS) has resulted in the development of hyponatremic seizures in people. This occurs as a consequence of antidepressant drug administration (such as citalopram).[12] At present, there are no such reports in horses.

Clinical Signs

Clinical signs of hyponatremia reported in horses include apparent blindness, loss of a menace response, and seizures.[6,13] The serum concentration of sodium necessary to initiate clinical signs is variable and depends upon both the severity of the hyponatremia and the duration over which the hyponatremia developed. Concurrent problems, such as hypoxia, hypoglycemia, or liver disease, may also alter the presentation of clinical signs associated with hyponatremia. In the experimental studies undertaken in rabbits, all acutely hyponatremic patients that developed hyponatremia within 2–3 hours, with sodium concentrations 119 ± 1 mEq/L, showed grand mal seizure activity and 86% of them died. All rabbits had moderate to marked cerebral edema with more than 17% increased brain water content compared to normonatremic controls. Rabbits with a slower development of hyponatremia (3.5 days), with a serum Na^+ 122 ± 2 mEq/L, were asymptomatic despite a 7% increase in brain water content. Rabbits with 16 days of hyponatremia, with a serum Na^+ 99 ± 3 mEq/L, were found to be weak, anorectic, lethargic, and unable to walk. These subjects also had a 7% increase in brain water content compared to normal controls.[14] The findings suggest that in hyponatremic patients, symptoms and morbidity are only grossly correlated with either magnitude or duration of hyponatremia and that the clinical signs may be referable to an interplay of increase in cerebral water content and concurrent losses of brain osmolytes.[14]

The serum sodium concentration was 99 mEq/L in one foal at the time of the seizures.[3] Correction of the same led to clinical improvement of clinical signs. The foal remained lethargic and depressed, with an absent menace when the serum sodium was 113 mEq/L. In another foal with diarrhea, seizures were observed with a concomitant serum sodium of 117 mEq/L.[13] Hyponatremia was also observed in 2 foals with rhabdomyolysis, with serum sodium values of 117–119 mEq/L, with no obvious neurologic abnormalities.[15] Hence it appears that the presence of neurologic signs is variable when the serum sodium is 115–120 mEq/L, and clinical signs are more reliably present when the values are <115 mEq/L. The clinical signs of acute hyponatremia in horses and humans include depression of the sensorium, depression of reflexes, seizure activity, respiratory arrest, and coma.

Treatment

Treatment of hyponatremia in horses can be achieved by the administration of hypertonic saline. The rapidity of correction is an important consideration in treatment, however. In human beings, demyelinating syndromes, such as central pontine myelinolysis (CPM) or extrapontine myelinolysis, can occur following the rapid restoration of serum sodium concentrations.[1,16] These can have severe consequences including major disability, a persistent vegetative state, or death. Risk factors identified for the development of CPM include chronic hyponatremia with rapid sodium restoration, concurrent hypokalemia, liver disease, a poor plane of nutrition, and cutaneous burns.[2,16] CPM is evident both histologically and on computed tomography.[17] One report showed that CPM occurs nearly in all patients treated for chronic hyponatremia with isotonic or hypertonic saline fluids.[18] The addition of furosemide and/or another diuretic agent significantly reduced the development of CPM and severe neurologic complications, as well as leading to a rapid sodium correction rate of 0.5 mEq/L/h or more.[18] No reports of CPM have been described in the horse however the potential for this should be considered in the treatment of horses. One of the editors Martin Furr (MF) has observed seizures in neonates immediately following apparently overly rapid correction of hyponatremia with hypertonic saline.

A gradual correction of blood sodium concentration is recommended rather than bolus dosing to prevent overcorrection and possible CPM. A dose of 2 mEq/kg/h, using hypertonic saline, has been suggested for humans,[19] but specific recommendations for horses have not been established. A potentially superior method is to calculate the sodium deficit, correcting the deficit with hypertonic saline to approximately 120 mEq/L of sodium by bolus infusion, followed by slow (over 24 hours) correction of

the remaining deficit. The sodium deficit is calculated as the difference between the measured and the desired serum sodium concentration times body weight (kg) times 0.6.[6] An empiric dose of 2 ml/kg of a 7.2% hypertonic saline solution has been used successfully in horses in addition to restricting the ingestion of electrolyte-free water.[6] Frequent monitoring of serum sodium concentration is important and should be done immediately after bolus treatment, then every 6–8 hours during sodium repletion. It has been recommended that in humans, the serum sodium correction should not exceed 15 mEq/L over the first 24 hours; this seems a prudent course in the case of the horse.[20] Complete resolution of clinical signs is expected, perhaps taking several hours. In cases with iatrogenic hyponatremia or psychogenic water drinking, fluid restriction with careful monitoring of serum electrolytes is utilized, providing there are no ongoing losses of total body fluid (i.e., diarrhea, renal failure). This conservative approach to therapy is useful in these particular situations.[21] Most conditions in the horse that result in hyponatremia are associated with excessive fluid loss, and therefore fluid restriction would be inappropriate.

Many reports advocate the use of furosemide in conjunction with hypertonic saline for treatment. Furosemide is useful as it limits treatment induced expansion of the extracellular fluid volume and induces diuresis equivalent to half-strength isotonic saline solution (i.e., low sodium excretion rates).[2] Dose rates for furosemide in horses are 0.5–1 mg/kg IV q 12–24 hours.

Most reported cases, as well as clinical experience, suggest that if the primary problem is resolved, long-term prognosis is good, with no observed sequelae.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration exceeding 144 mmol/L.[3–5] This electrolyte derangement represents a deficit of water in relation to the body's sodium stores. It is common and occurs secondary to excessive ingestion/administration of sodium or through excessive loss of body water.[2] Neurologic manifestations of hypernatremia are rarely seen in horses, but the finding is frequently observed when evaluating serum biochemistries in the horse.

Brain shrinkage caused by hypernatremia can cause vascular rupture, cerebral bleeding, subarachnoid hemorrhage, and permanent neurologic damage or death. Shrinkage occurs secondary to a flux of water out of the tissue. An adaptive response of the central nervous system (CNS) exists whereby the shrunken brain gains additional solute, and tissue restitution occurs when water moves back in following therapy. This response leads to normalization of brain volume. Slow correction of a hypertonic state reestablishes a normal brain volume and osmolarity, usually without inducing cerebral edema. The risk of rapid correction is that excessive water moves into a hypertonic brain interstitium, and cerebral edema develops.[2]

Severe fatal hypernatremia has been described in a 2-year-old Standardbred gelding secondary to an ependymoma of the neurohypophysis, which was suspected of causing impingement on the thirst centre of the brain.[22] However, many disease states causing a loss of total body water such as severe dehydration due to illness or water deprivation can result in hypernatremia in the horse.

Clinical signs largely reflect central nervous system dysfunction and are prominent when the rise in serum sodium concentration is rapid (over a few hours) or large. General signs include hyperpnea, muscle weakness, restlessness, insomnia, lethargy, and intense thirst. Orthostatic hypertension and tachycardia are observed secondary to hypovolemia. Reported neurologic signs in the horse are prolapsed nictitating membrane, myoclonus of the facial, neck and forelimb musculature, altered consciousness that is directly proportional to the severity of hypernatremia, persistent tail swishing, and coma.[22]

Treatment

Two key concepts must be addressed in treating hypernatremia; correcting the hypertonicity and managing the underlying causes.[2] Demyelinating syndromes are also observed in chronically affected hypernatremic patients following the rapid restoration of serum sodium concentration to within the normal reference range.[1]

Correcting the hypertonicity

Acute cases (rapid development of hypernatremia):

- Aim to lower the serum sodium concentration to 140–145 mmol/L.
- Preferred route is enteral, although parenteral routes are suitable alternatives.

- Fluid (Infusate) types: water, 0.25% NaCl (quarter strength), 0.45% NaCl (half strength), 5% dextrose.
- The more hypotonic the infusate solution, the slower the rate of administration needs to be.
- The rate of infusate administration should be calculated using Formula 21.1[1] given below.

$$\text{Change in serum } Na^+ = \frac{\text{Infusate } Na^+ - \text{serum } Na^+}{[BW(kg) \times 0.6] + 1} \quad (21.1)$$

In acute cases, the aim of therapy should be to reduce the serum sodium concentration by 1 mmol/L/h.

Chronic cases:

- Aim to lower the serum sodium concentration to 140–145 mmol/L.
- Preferred route is enteral; parenteral is a suitable alternative.
- Fluid (Infusate) types: water (enterally only), 0.25% NaCl (quarter strength), 0.45% NaCl (half strength), 5% dextrose.
- The more hypotonic the infusate solution, the slower the rate of administration needs to be.

In chronic cases, the aim of therapy should be to reduce the serum sodium concentration by no more than 0.5 mmol/L/h (~10 mmol/L/day) to prevent cerebral edema

Follow-up to be done with hourly assessments of serum electrolyte concentrations until levels are within the normal ranges to prevent overcorrection and possible development of cerebral edema.

POTASSIUM

Potassium is the major intracellular cation and is important for several biochemical functions. Approximately, 98% of the total body's potassium is intracellular. In contrast, potassium in the extracellular fluid represents <2% of whole body potassium content. Of this extracellular fraction, only ~0.4% is measurable in the serum.[23] The ratio of intracellular to extracellular potassium concentration is of critical importance for the maintenance of the resting membrane potential and production of action potentials in excitable nervous tissue.[24] This potential difference across cell membranes is maintained by the activity of the sodium-potassium adenosine triphosphate enzyme pump (Na-K ATPase) by actively pumping Na^+ out of the cell in exchange for K^+.[25]

Horses normally ingest a large amount of potassium in feed. The average horse consuming timothy/alfalfa hay consumes ~4000 mM K^+/day.[26] In hospitalized human patients, disorders of potassium represent the most common electrolyte abnormalities observed,[23] which may also be true of hospitalized horses.

Most disorders of potassium can be attributed to one of three mechanisms: problems with potassium intake (relatively too much or too little (more common)), abnormalities of potassium distribution between the intracellular and extracellular spaces, or abnormalities of potassium excretion.

Hypokalemia

Hypokalemia is defined as serum potassium ion concentration below the normal range (3.5–4.5 mEq/L).[3–5] Hypokalemia is often observed in routine clinical chemistry profiles in high risk patients, but clinical manifestations are rarely observed. The likely explanation for this is that intracellular concentrations are probably normal.

Hypokalemia results in hyperpolarization of the cell membrane leading to prolongation of the action potential and refractory period. This manifests as varying degrees of muscle weakness and occasionally complete paralysis.

Johnson *et al*. (1991) showed that adult horses subjected to forced anorexia over a seven day period had a reduction in skeletal muscle potassium concentration from 91.06 mmol/L at day 0 to 73.62 mmol/L at day 7, with a change in resting membrane potential favoring hyperpolarization from day 0 to day 7 (–105.84 mV and –100.93 mV respectively). This highlights the critical role of dietary intake in the horse.[26]

Hypokalemic myopathy can occur in any species including horses. Affected animals may show ventroflexion of the neck, muscular weakness, exercise intolerance, a stiff gait, and sometimes pain on palpation of affected muscle groups.[26,27]

Potential causes of potassium depletion include concurrent hypomagnesemia where Mg^{++} acts as a cofactor for the Na-K ATPase pump, thereby causing reduced intracellular K^+ concentrations and increased intracellular Na^+ concentrations. Other causes include food deprivation, severe anorexia, or those with a physical inability to ingest food. The

total whole body potassium content is estimated to be 28,000–30,000 mM of which 10–13% can be lost during several days of anorexia.[23,26] Clinical conditions promoting potassium loss include diarrhea, excessive nasogastric/enterogastric reflux, acid–base imbalance, endotoxemia, hyperhidrosis, and renal dysfunction.

Lactation represents a significant drain of potassium stores in the mare, as mare's milk has a high potassium concentration. This is usually not a problem in mares that are eating well (Table 21.1).

Diagnosis

Diagnosis is based on clinical signs, evidence of pre-existing disease, particularly anorexia, renal and GI disease, and measurement of serum potassium concentration. This assays extracellular potassium concentration that which correlates poorly with intracellular concentrations. The measurement of the intracellular potassium concentration is difficult and impractical in the clinical setting.

Assessment of renal function may be prudent, especially in cases where dietary intake and no other systemic clinical signs are evident and inappropriate excretion is suspected. Measuring the fractional excretion of K^+ may provide an indication of inappropriate excessive potassium excretion.

Electrocardiographic (ECG) changes associated with hypokalemia include increased P-wave amplitude, prolongation of the P-R interval, Q-T interval prolongation, reduced T-wave amplitude, and T-wave inversion.[23] These changes can arise in any number of clinical situations leading to hypokalemia.

Treatment

Oral and intravenous preparations of potassium salts (usually potassium chloride or potassium iodide) are available. It is important to consider current deficits, ongoing losses, maintenance requirements, and sequestration.

One can use Formula 21.2 given below to calculate an extracellular potassium deficiency:

$$\begin{aligned} &K^+ \text{ (mEq) deficit} \\ &\quad = 0.3 \times \text{body weight in kilograms} \\ &\qquad \times (4.0 - \text{measured serum } K+) \end{aligned} \qquad (21.2)$$

where 0.3 is the extracellular fluid volume, and 4.0 is a desired serum potassium concentration.

It is important that the intravenous potassium administration rate does not exceed 0.5 mEq/kg/h. Intravenous fluids containing glucose and bicarbonate or bicarbonate precursors (lactated Ringer's solution) will exacerbate measurable hypokalemia by promoting intracellular movement.

Table 21.1. Clinical Signs of Hypokalemia in the Horse

Severity	Clinical Signs
Mild	Apparent tiredness, lethargy, mild muscle, weakness
Moderate	Prominent muscle weakness, dysrhythmias
Severe	Rhabdomyolysis, myoglobinuria, paralysis, respiratory arrest, fatal dysrhythmias

Hyperkalemia

Hyperkalemia is a serious, potentially life-threatening electrolyte abnormality. Hyperkalemia is defined as a serum potassium concentration greater than 4.5 mEq/L.[3–5] Increased serum potassium concentration reduces the activity of excitable membranes, especially in cardiac muscle, but also skeletal muscle and neurons. Excessive extracellular K^+ causes cardiac flaccidity and decreases the conduction of action potentials through the atrioventricular (AV) node.[23,25] Heart rate and cardiac output subsequently decrease. The effects of hyperkalemia on skeletal muscle are varying degrees of muscle fasciculations and weakness, which may be severe enough to cause complete paralysis and cardiac arrest.

Disorders related to excessive ingestion of potassium are rare, especially if the horse has normal renal function. More commonly, hyperkalemia is linked to the genetic condition hyperkalemic periodic paralysis (HYPP), secondary to uroperitoneum, or over-administration during supplementation.

Hyperkalemia is a common finding in foals with a ruptured urinary bladder and subsequent uroperitoneum. Mare's milk has a high K^+ concentration, and consequently, foal urine similarly has a high K^+ concentration. K^+ in the free abdominal fluid can be absorbed across the peritoneum causing significant increases in the serum K^+ concentration. This is a

medical emergency, and reducing the serum K^+ concentration should be addressed prior to surgical correction.[28,29]

Massive blood transfusion of stored blood or diseases causing widespread intravascular hemolysis can cause an increase in serum potassium concentration.[23]

Severe signs are usually not apparent until serum K^+ exceeds 7.0 mEq/L, although early ECG changes may be present at concentrations >6.0 mEq/L.[23,28] These can include cardiac conduction disturbances with risk of sudden death in addition to neuromuscular signs. The *classic* ECG findings in horses with hyperkalemia include flattening to absent P waves, prolongation of the P-R interval, widening QRS complexes with a bizarre *sine wave* appearance, and finally ending in ventricular asystole or fibrillation at serum levels around 8–10 mEq/L.[23,26]

Hyperkalemic Periodic Paralysis (HYPP) "Impressive Disease"

Affected breeds include Quarter horses, Paint horses, Appaloosas, and any horse carrying bloodlines traceable to the sire *Impressive*. It is not known if the mutation in this stallion was inherited or spontaneously occurred. The typical phenotype of affected horses includes horses that are heavily muscled. HYPP is homologous to the human genetic disorder adynamia episodica hereditaria or Gamstorp's disease, first reported in humans in 1950.[30]

Pathophysiology

HYPP is a genetic condition with an autosomal dominant mode of inheritance.[31,32] There is variable penetrance or expression of the phenotype among horses, and co-dominance exists. Episodes are characterized by intermittent attacks of weakness and/or paralysis. The precipitating factors identified include: high K^+ diet, fasting, cold weather, and rest after strenuous exercise.

The genetic defect affects the sodium channel of the muscle cell membrane. The mutation is an amino-acid substitution where phenylalanine is substituted for leucine in the transmembrane domain IVS3 of the α-subunit of the sodium channel.[31,33] This was confirmed in 1995 using PCR genomic DNA amplification in affected cell lines.[33]

Defective Na^+ voltage-gated channels increase Na^+ membrane conductance, due to defective inactivation.[31] The primary physiological defect in mutant Na^+ channels is an impairment of channel inactivation. It is manifested as bursts of persistent activity during which the channel closes and opens throughout a maintained depolarization.[33] When the serum K^+ level rises, this further increases Na^+ conductance leading to muscle membrane depolarization and efflux of intracellular K^+, therefore a concurrent hyperkalemia is measured in serum during these episodes. However, normal horses undergoing intensive exercise may also have serum K^+ levels comparable to those affected with HYPP thereby suggesting that potassium levels by themselves are not responsible for the clinical signs.[31]

As the neuronal cell membrane depolarizes and approaches the threshold potential, it becomes hyperexcitable, which is manifested as myotonic activity. As subsequent depolarization occurs, the muscle cell membrane becomes refractory, and paralysis occurs.[31]

Gene nomenclature classifies homozygous normal horses as NN, heterozygotes as NH, and homozygous affected as HH. Spier *et al.* (1995) conducted genetic surveying and found that the gene-positive frequency (of H) in the Quarter horse population (based on testing 20,000 samples) is 4.4%.[34] Both HH and NH genotypes can be affected by HYPP attacks.[31] However, HH genotypes are generally more severe and many die. In one report, a 7-month-old Quarter horse filly developed myotonia, fasciculations, and sweating, with a concurrent hyperkalemia 150 minutes after the induction of general anesthesia (maintained with halothane). This filly was heterozygous (NH) on subsequent DNA testing.[35]

Clinical Signs

Clinical signs in the horse usually begin by the age of 3 years and are recurrent in nature.[31,33]

Table 21.2 lists the clinical signs that may be observed from the early stages through to the more pronounced signs.

Horses are typically conscious and alert to visual, audible, and tactile stimuli. Episodes typically last for 30–60 minutes (range 20–240 minutes). Interestingly, the resting membrane potential tends to become more negative with increasing age; so the number of clinical episodes appears to decrease with age.

Diagnosis

Genetic testing using DNA from equine hair bulbs or whole blood is performed. Tests are reported as

Table 21.2. Clinical Signs of HYPP in the Horse

Mild Signs	Pronounced Signs
Prolapsed nictitans membrane (often a first sign of an impending attack)	Buckling of the forelimbs progressing to complete recumbency
Generalized muscle tension	Marked muscle fasciculations
Sustained contraction of the muzzle and drooling	
Facial spasm	Altered phonation with audible stridor (laryngeal paresis)
Sweating	Diminished tendon reflexes
Fasciculations over the shoulder, flanks and neck	Sudden death (due to cardiac arrest and/or respiratory failure)
Myotonia in response to percussion (finger-flick test)	
Buckling of the forelimbs	

N/N (normal), N/H (heterozygous or carrier), or H/H (affected). If a suspect animal dies suddenly, collection of hair sample and genetic testing is recommended, especially if that animal has progeny with unknown status. Also, aqueous humor samples for K^+ testing may support hyperkalemia at the time of death.

Provocative K^+ challenge testing can be done, however adverse affects including death make this method of testing no longer necessary nor appropriate.

It is important to recognize that the American Quarter Horse Association (AQHA) will only recognize test results performed through an approved, licensed laboratory. These include the Veterinary Genetics Laboratory at The University of California, Davis (www.vgl.ucdavis.edu) and DDC Veterinary Diagnostics Center, Fairfield, OH (www.vetdna center. com). Additional testing laboratories recognized by the AQHA can be found on their website (www.aqha.org)

Serum K^+ levels can be normal but are often elevated, usually around 5.0–11.7 mEq/L. Episode recovery is related to normalization of serum K^+ concentration. Serum CK and AST activities are often normal or mildly elevated.[30,31]

Microscopic findings on muscle biopsy typically show no abnormalities at the light microscope level. There is usually a lower intracellular K^+ concentration and higher intracellular H_2O content. No distinguishing features are observed in fiber architecture. These contrast with paramyotonia syndromes in humans where dilated sarcoplasmic reticulum, fusion of T-tubules, and focal fiber destruction yield a vacuolar myopathy.

Electromyography (EMG) abnormalities can be observed at rest and during an episode. Complex repetitive discharges, in addition to myotonic potentials, fibrillation waves, and positive sharp waves can be seen.[31] Insertional and resting activity (myopotentials) can be observed in clinically normal or affected animals. Prolonged insertional activity is pronounced as well as spontaneous myotonic discharges in doublets or triplets.[33]

Management

Acute Episodes

Mildly affected horses:

- Light exercise only. Feed a readily available soluble carbohydrate (oats, Karo syrup (*not molasses*—high K^+ content)) to promote insulin-mediated cellular uptake of potassium.
- Acetazolamide (3 mg/kg PO) may be useful.[31,37,38]

Severely affected horses (recumbent):

- Administer 5% dextrose solution IV with sodium bicarbonate (with or without insulin) to promote intracellular movement of K^+.
- Protamine Zn insulin.
- Calcium gluconate—23% (0.2–0.4 mg/kg) diluted in 1–2 L 5% dextrose, slow IV has also been used.

- Bicarbonate therapy: *Do not mix with calcium containing solutions*.
- Separate IV access preferable. (0.5–2 mEq/kg slow IV).

Prevention of future attacks may be achieved using daily administration of acetazolamide at 2–2.2 mg/kg PO q 12 h. Acetazolamide is a carbonic anhydrase inhibitor and potassium-wasting diuretic. The mechanisms underlying the beneficial effects of acetazolamide both in preventing and attenuating HYPP episodes is not clear, but a group of researchers indicated that acetazolamide can activate skeletal muscle calcium-activated potassium channels.[39] Activation of these channels increases the hyperpolarization phase between bursts of action potentials reducing the excitability of the muscle cell. In addition, acetazolamide has been shown to stabilize blood glucose and potassium by stimulating insulin secretion.[37–39] Avoid feeding alfalfa hay, more frequent feedings especially with grains (higher soluble carbohydrate stimulus), and K^+ containing salt-licks, and provide regular mild exercise. Establish a set feeding and exercise regime, and avoid sudden changes. Pasture turnout may be beneficial.

Prognosis is considered good, although as in humans, permanent myopathy with weakness may occur. Episodes are unpredictable, therefore only experienced persons with a knowledge of the symptoms should ride affected horses. Less-experienced riders, or people unfamiliar with the condition should not ride the horse to prevent inadvertent injury.

CALCIUM

Hypocalcemia

Hypocalcemia is defined as serum ionized calcium (iCa) concentration below the normal range (6–7 mg/dL).[40] An extensive list of disease-states causing hypocalcemia has documented in the horse and can be found in Table 21.3.

Clinical Signs

The clinical signs associated with hypocalcemia in the horse are related to magnitude of the hypocalcemia. Mild hypocalcemia results in increased excitability, while more severe hypocalcemia results in tetanic spasms and mild incoordination, which can progress to recumbency and stupor in severe cases. Mild clinical signs are considered to occur at 8–10 mg/dl, moderate signs at 5–8 mg/dl, and severe signs below 5 mg/dl of serum total calcium.[55]

Table 21.3. Conditions Leading to Hypocalcemia

Hypoparathyroidism (rare)[41,42]
Eclampsia (*Lactation Tetany*)[27,43]
Idiopathic hypocalcemia of foals[44]
Exercise-induced hypocalemia[45,46]
Disease-states causing endotoxemia[47,48]
Oxalate ingestion[49]
Cantharadin toxicity[50]
Acute renal failure[41]
Pancreatic necrosis
Colic and other GI disease[51–53]
Transportation *Transport Tetany*
Liver disease
Iatrogenic bicarbonate overdose
Furosemide administration[54]
Sepsis[47,48]

Clinical signs are related to increased neuromuscular excitability and decreased smooth muscle contractility. Extracellular iCa concentrations affect the voltage at which the Na^+ channels in nerve fibers open causing an action potential. Broadly speaking, calcium ions bind to neuronal Na^+ channels, decreasing the permeability of Na^+ influx and increasing the voltage required to open these fast Na^+ channels. When the iCa concentrations are low, neuronal membrane threshold for an action potential is decreased, making neuronal tissue *more excitable*. This is often manifested as *tetany*, whereby continued and repeated electrical discharging of the neuromuscular unit occurs.[25,40]

Seizure activity can also occur in addition to the more commonly observed peripheral neuropathies. Seizures were observed in 4 neonatal foals with hypocalcemia and total serum calcium concentration of 5.2–6.3 mg/dl.[44] Reduced extracellular iCa concentrations increase the CNS neuroexcitability. Foals are reported to develop hypocalcemic seizures,[44] usually secondary to septicemia or idiopathic hypocalcemia. Many respond favorably to exogenous administration of calcium, and this ameliorates the clinical signs. In adults, the prognosis for hypocalcemic seizures are more guarded. [40,44,56] Specific manifestations of ionized hypocalcemia in the horse include synchronous

diaphragmatic flutter (thumps), whereby depolarization of the right atrium stimulates neuronal discharge of the phrenic nerve as it crosses over the heart. Clinically, this is observed as a rhythmic movement of the flank as a result of diaphragmatic contractions that are synchronous with the rhythm of the heart.[42,45]

Excessive chloride ion losses in the horse can lead to an ionized hypocalcemia. Hypochloremic metabolic alkalosis leads to an increased binding of Ca^{++} to blood transport proteins (mainly albumin). This is particularly important for sport horses with excessive perspiration, for example, endurance athletes. Excessive respiration and consequent respiratory alkalosis in these exercising horses can also contribute to the development of ionized hypocalcemia.[40,42,45]

Lactation tetany (eclampsia) typically occurs in horses in the last 2–3 weeks of pregnancy and up to 5 days after weaning. Draft breeds appear to be overrepresented, however any mare producing large volumes of milk, eating a low-calcium ration or grazes lush pasture, and performs physical activity is at increased risk. Many times, these mares show mild clinical signs in addition to hypersalivation, dysphagia, and hyperhidrosis.[27,43] Additional clinical signs seen in mares with lactation tetany include anxiety, muscle fasciculations, tachypnea, ataxia, and tremors.

Hypocalcemia related to parathyroid gland dysfunction has been rarely reported in horses. Primary glandular parathyroid hormone (PTH) production can be depressed (hypoparathyroidism) causing hypocalcemia,[42] hyperphosphatemia (related to reduced urinary fractional excretion of phosphorus), and hypomagnesemia and has been reported in the horse.[41] Secondary hypoparathyroidism has not been reported in the horse, however low PTH concentrations have been demonstrated in septic horses, attributed to a concurrent hypomagnesemia.[42] Inflammatory mediators in septic/endotoxemia shock may also contribute to reduced PTH release and subsequent hypocalcemia.[57–60] A complete understanding of the mechanisms of hypocalcemia in sepsis is still unclear.

In foals, idiopathic hypocalcemia[44] and hypocalcemia secondary to excessive oxalate ingestion[49] has been described. Foals may show tachycardia, hyperhidrosis, diarrhea, muscle rigidity, stiff gait, and sometimes seizure activity with opisthotonus.[44] Idiopathic hypocalcemia has been observed in adult horses on grass pasture.

Acute renal failure also causes hypocalcemia and hypomagnesemia where functional proximal tubular epithelial cells are required to reabsorb filtered Ca and Mg. When toxic or hypoxic injury occurs causing acute tubular necrosis, re-absorption is hindered and these electrolytes are voided in the urine.

Diagnosis

Diagnosis is based on clinical signs, evidence of concurrent or pre-existing disease, and assay of total and ionized calcium concentrations. Fractional excretion of calcium has been described in normal horses ($3.4 \pm 2.6\%$).[61] Sequential measurement of fractional excretion of calcium has been used in the management of horses with recurrent idiopathic hypocalcemia.

EMG changes can be observed with subclinical hypocalcemia and show positive sharp waves, fibrillation potentials in doublets, triplets, and multiplets. An increase in polyphasic motor unit action potentials is also seen. These findings are indicative of nerve hyperirritability.[62]

Treatment

The aim of treatment is to correct serum calcium to a normal concentration. During treatment with calcium, it is necessary to consider the magnitude of the deficit, maintenance requirements, ongoing losses, and sequestration (or third spacing). Despite the inciting cause, significant losses can be expected to occur from normally functional kidneys. This is particularly important in even subtle cases of hypocalcemia as many sick horses will have a diminished calcium intake due to inappetance and anorexia. It is good practice to supplement anorexic horses with calcium as hypercalcemia from excessive administration is rare if the horse has normal kidney function. Calcium gluconate (50 ml of a 23% solution per 5 L crystalloids) can be administered with little risk.

The ionized calcium deficit can be calculated using Formula 21.3 given below:[40]

$$\frac{(6.5 - \text{measured iCa}) \times 10 \times 0.3 \times (\text{body weight in kg})}{\text{iCa ratio}} \qquad (21.3)$$

where 6.5 is the desired iCa, 10 is a multiplication factor, 0.3 is the extracellular fluid volume, and the iCa ratio is the total Ca concentration divided by the iCa concentration.

In situations in which ionized calcium cannot be determined, total serum calcium can be used as a rudimentary indicator of the iCa concentration; however, the total can vary widely with changes in plasma albumin concentration. It is best to interpret total calcium concentrations concurrently with the plasma albumin concentration. Measuring the iCa concentration provides the most accurate assessment of biologically active body calcium.

The calculated calcium deficit can be corrected with a variety of methods. Administering 2 mg Ca/kg/h, which is approximately 50 cc of a 23% calcium gluconate solution for a 500 kg horse, can treat mild hypocalcemia; this dose can be diluted in 5 L of crystalloid solution. For severe hypocalcemia, doses up to 5–6 mg Ca/kg/h have been used. Calcium gluconate 23% can be given at 250–500 ml per 500 kg horse slow IV, or IM. For lactation tetany, calcium borogluconate with magnesium at 250 ml per 450 kg body weight can be given slowly IV. In severely hypocalcemic horses, the heart rate and rhythm should be monitored during treatment, and the rate slowed or stopped if irregularities are noted. Do not administer calcium solutions in the same IV line as bicarbonate solutions, as the mixture may cause precipitation and potentially thromboembolic disease.

Oral supplementation with calcium chloride salts, calcium carbonate (limestone), or dicalcium phosphate are valid options in mild cases, however for severe cases or where gastrointestinal disease may reduce absorption (e.g., enterocolitis), systemic parenteral preparations are advised. A reasonable oral dose is 0.3–0.5 g/kg.

MAGNESIUM

In horses, magnesium is the fourth most abundant cation in the body, and 65–80% of serum magnesium assayed is in the ionized form. The majority of magnesium is bound and stored within the hydroxyapatite framework of bone (50–60%). Less than 1% of total body magnesium is in the extracellular space; therefore, serum Mg^{++} concentrations are not a reliable indicator of magnesium status in the body. The diet usually supplies adequate magnesium for absorption through metabolic and hormonal mechanisms. In the horse, 25% of ingested Mg is absorbed from the proximal 50% of the small intestine, 35% from the distal small intestine, and 5% from the GI tract, distal to the ileum.[63–65]

Magnesium acts as a membrane stabilizer, promotes competent neuronal conduction, ion transportation, and regulates calcium channel activity. Mg^{++} is required for normal function of the Na-K ATPase and Ca-K ATPase pumps that regulate intracellular potassium concentrations by acting as a co-factor for activation. Magnesium is therefore an important element for excitable tissues. The effects of defective ATPase pumps and ion channel dysfunction include changing the resting membrane potential of excitable tissues, deranged electrochemical gradients, derangement in maintaining electroneutrality, and disturbing repolarization of neural and cardiac tissues.[66,67] In contrast to the role of calcium on the neuron, magnesium causes blockade of neurotransmitter-release at the neuronal synapse.[68] Magnesium is also vital in the normal function of smooth muscle myocytes of gastrointestinal tissues and the muscular tunic of peripheral vasculature, as well as the cardiomyocytes modulating cardiac contractile strength.[69,70] Hypomagnesemic conditions are well described in the literature, whereas hypermagnesemic conditions are rarely encountered. The normal reference range for serum magnesium in the horse is 0.53–2.28 mmol/L (total serum magnesium) or 0.46–0.66 mmol/L (ionized).[3,40]

Hypomagnesemia

Hypomagnesemia is well described in large animals including horses and is often related to inadequate dietary intake. Though normally affecting ruminants, there are reports of horses with primary hypomagnesemia.[71,72] The syndrome is classically observed where animals are feeding exclusively on fresh green (rapidly growing) pastures that are low in magnesium content. Severe hypomagnesemia can result in neuromuscular disturbances; however, these are rare in the case of horse.[73] The severity of hypomagnesemia is related to decreased dietary intake, excessive mobilization of endogenous stores, and increased urinary clearance of Mg^{++}.[73]

Early clinical signs include restlessness, extreme alertness, muscular weakness, and muscular fasciculation. Some animals then become excitable, aggressive, and belligerent. External stimulation may cause extreme tetanic episodes as well as marked ataxia and vocalizing. Severely affected animals become recumbent and may show opisthotonus and paddling

movements. Seizure activity, ventricular fibrillation, coma, and sudden death can result in severe cases.[27,73,74]

Cardiac rhythm disturbances can occur and include ventricular dysrhythmias, supraventricular tachycardia, and atrial fibrillation. ECG findings characteristic of hypomagnesemia include prolongation of the P-R interval, ST-segment depression, peaked T waves, and widening of the QRS complex.[40] Hypomagnesemia and concurrent hypokalemia are frequent observations. The ability of Mg^{++} to act as a coenzyme for the Na-K ATPase pump leads to depletion of intracellular K^+ concentration and increased intracellular Na^+ concentration.[75] This lowers the resting membrane potential facilitating spontaneous depolarization activity and impairment of action potential propagation. This phenomenon has been demonstrated in studies on Purkinje fiber function, where increased excitability can lead to the development of dysrhythmias.[69,70,75]

Studies in foals fed with magnesium-deficient diet have shown that overt nervousness, tetany in response to loud noises, muscular tremors, and ataxia are consistent findings. Some of these foals became comatose, some exhibited hyperhydrosis, and/or seizure activity, and some died. Necropsy evaluation consistently revealed severe aortic and pulmonary artery elastin fiber mineralization when fed a Mg-deficient ration on a chronic basis (>1 month). The total serum magnesium concentrations at which these severe neurologic signs occurred was 0.7 ± 0.4 mg/dL.[73]

Meijer (1982) reported the occurrence of concomitant hypocalcemia and hypomagnesemia in two Thoroughbred broodmares, whereby transportation and nursing were identified as precipitating causes of tetany. The total serum magnesium level in these horses was 1.0 and 1.9 mg/dL in addition to both having markedly low total serum calcium concentrations (4.0 and 5.4 mg/dL, respectively). They both responded favorably to the administration of calcium borogluconate and magnesium chloride, intravenously.[74]

Several horses with a history of intermittent abherrant behavior and ataxia have been found to have low serum magnesium concentrations as observed by one of the editors (MF). The clinical signs have resolved with magnesium supplementation. Hence, assessing serum magnesium concentration is warranted in horses with such problems.

Diagnosis

Diagnosis of hypomagnesemia is based on clinical signs and assay of total and ionized magnesium concentrations.[72] Ionized magnesium is probably a more accurate assessment of Mg status in the horse and is the biologically active form.

EMG changes have been observed in subclinical hypomagnesemic horse and are identical to the changes observed in subclinical hypocalcemia. These changes represent nerve hyperirritability.[62]

Treatment

The recommended dose rate for magnesium sulfate is 25–150 mg/kg/day as a 5% solution in 0.9% sodium chloride or other polyionic balanced electrolyte solution, intravenously. Continuous rate infusions of $MgSO_4$ can be given at 150 mg/kg/day IV. Commercial crystalloid solutions are typically lacking in adequate magnesium content with Plasmalyte-148 (Baxter Healthcare, Deerfeld, IL) and Normosol-R (Abbott Laboratories, North Chicago, IL) containing no magnesium. Oral supplementation with magnesium sulfate can be achieved by giving 1–2 ounces per horse/day as a feed top-dress.

Hypermagnesemia

Very few reports of hypermagnesemia are found in horses, with no well described syndromes of primary hypermagnesemia. One case report describes hypermagnesemia in 2 horses treated for large colon impaction colic using magnesium sulfate ($MgSO_4$) and dioctyl sodium succinate (DSS). Both horses received less than 2 times the normal dosage administration of $MgSO_4$. These animals showed transient weakness, flaccid paralysis, recumbency, tachycardia, tachypnea and had serum total Mg concentrations 5 times the reported reference range. The horses were treated with calcium gluconate on several occasions and they recovered completely.[76] It was speculated that the combination of cathartics with DSS may have enhanced systemic absorption of Mg^{++} and led to the clinical signs.

REFERENCES

1. Soupart A, Decaux G. 1996. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications. *Clin Nephrol* 46:149–56.
2. Adrogue HJ, Madias NE. 2000. Hyponatremia. *N Eng J Med* 342:1581–9.

3. Navarro M, Monreal L, Segura D, *et al*. 2005. A comparison of traditional and quantitative analysis of acid-base and electrolyte imbalances in horses with gastrointestinal disorders. *J Vet Intern Med* 19:871–7.
4. Johnson PJ. 1995. Electrolyte and acid–base disturbances in the horse. *Vet Clin North Am Equine Prac* 11:491–514.
5. Constable PD, Hinchcliff KW, Muir WW III. 1998. Comparison of anion gap and strong anion gap as predictors of unmeasured strong ion concentration in plasma and serum of horses. *Am J Vet Res* 59:881–7.
6. Lakritz J, Madigan J, Carlson GP. 1992. Hypovolemic hyponatremia and signs of neurologic disease associated with diarrhea in a foal. *J Am Vet Med Assoc* 200:1114–6.
7. Szolnoki JM, Puskas F. 2006. Hyponatremic seizures after suprapubic catheter placement in a 7-year-old child, *Paediatr Anaesth* 16:192–4.
8. Duke T, Kinney S, Waters K. 2005. Hyponatremia and seizures in oncology patients associated with hypotonic intravenous fluids. *J Paediatr Child Health* 41:685–6.
9. Dowling PM, Williams MA, Clark TP. 1993. Adrenal insufficiency associated with long-term anabolic steroid administration in a horse. *J Am Vet Med Assoc* 203:1166–9.
10. Kuz GM, Manssourian A. 2005. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother* 39:1943–6.
11. Das P, Carcao M, Hitzler J. 2005. DDAVP-induced hyponatremia in young children. *J Paediatr Hematol Oncol* 27:330–2.
12. Flores G, Perez-Patrigeon S, Cobos-Ayala C, *et al*. 2004. Severe symptomatic hyponatremia during citalopram therapy: a case report. *BMC Nephrol* 5:2.
13. Kortz GD, Madigan JE, Lakritiz J, *et al*. 1992. Cerebral oedema and cerebellar herniation in four equine neonates. *Equine Vet J* 24(1):63–6.
14. Arieff AI, Llach F, Massry S. 1976. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore)* 55(2):121–9.
15. Perkins G, Valberg SJ, Madigan JM, *et al*. 1998. Electrolyte disturbances in foals with severe rhabdomyolysis. *J Vet Intern Med* 12:173–7.
16. Sterns RH, Riggs JE, Schochet SS. 1986. Osmotic demyelination syndrome following correction of hyponatremia. *N Eng J Med* 314(24):1535-42.
17. Ayus JC, Krothapalli RK, Arieff AI. 1987. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N Eng J Med* 317(19):1190–5.
18. Cluitmans FH, Meinders AE. 1990. Management of severe hyponatremia: rapid or slow correction?. *Am J Med* 88(2):161–6.
19. Ayus JC, Olivero JJ, Frommer JP. 1982. Rapid correction of severe hyponatremia with intravenous hypertonic saline solution. *J Am Med Assoc* 72:43–8.
20. Singer GG, Brenner BM. 2004. Fluid and Electrolyte Disturbances, In *Harrisions Principles of Internal Medicine*, 16th edition. edited by Kasper DL, Fauci AS, Longo DL, *et al*. New York, NY: McGraw-Hill Company.
21. Goh KP. 2004. Management of hyponatremia. *Am Fam Physician* 69(10):2387–94.
22. Heath SE, Peter AT, *et al*. 1995. Ependymoma of the neurohypophysis and hypernatremia in a horse. *J Am Vet Med Assoc* 207(6):738–41.
23. Shaefer TJ, Wolford RW. 2005. Disorders of potassium. *Emerg Med Clin N Am* 23:723–47.
24. Zull DN. 1989. Disorders of potassium metabolism. *Emerg Med Clin N Am* 7(4):771–94.
25. Guyton AC, Hall JE. 2000. Membrane potentials and action potentials. In *Textbook of Medical Physiology*, 10th Edition, 55–60. Philadelphia, PA: Saunders.
26. Johnson PJ, Goetz TE, *et al*. 1991. Effect of whole-body potassium depletion on plasma, erythrocyte, and middle gluteal muscle potassium concentration of healthy, adult horses. *Am J Vet Res* 52(10):1676–83.
27. Lorenz MD, Kornegay JN. 2004. Disorders of voluntary movement. In *Handbook of Veterinary Neurology*, 4th Edition, 202, 265–70. Philadelphia, PA: Saunders.
28. Bryant JE, Gaughan EM. 2005. Abdominal surgery in neonatal foals. *Vet Clin North Am Equine Pract* 21:523–5.
29. Richardson DW, Kohn CW. 1983. Uroperitoneum in the foal. *J Am Vet Med Assoc* 182:267.
30. Cox J. 1985. An episodic weakness in four horses associated serum hyperkalemia and the similarity of the disease to hyperkalemic paralysis in man. *Proc Am Assoc Equine Pract* 31:383.
31. MacLeay JM. 2004. Disorders of the musculoskeletal system, In *Equine Internal Medicine*, 2nd Edition, edited by Reed, Bayley & Sellon, 494–6, Philadelphia, PA: Elsevier.
32. Naylor JM, Robinson JA, *et al*. 1992. Inheritance of myotonic discharges in American Quarterhorses and the relationship to hyperkalemic periodic paralysis. *Can J Vet Res* 56(1):62–6.
33. Cannon SC, Hayward LJ, *et al*. 1995. Sodium channel inactivation is impaired in equine hyperkalemic periodic paralysis. *J Neurophysiol* 73(5): 1892–9.

34. Spier S, Valberg V, *et al*. 1995. Update on hyperkalemic periodic paralysis. Proceedings of the 41st American Association of Equine Practitioners meeting, Lexington, KY, 231.
35. Bailey JE, Pablo L, Hubbell JA. 1996. Hyperkalemic periodic paralysis episode during halothane anesthesia in a horse. *J Am Vet Med Assoc* 208(11):1859–65.
36. Robinson JA, Naylor JM, Crichlow EC. 1990. Use of electromyography for the diagnosis of equine hyperkalemic periodic paresis. *Can J Vet Res* 54(4):495–500.
37. Beech J, Lindborg S. 1995. Prophylactic efficacy of phenytoin, acetazolamide and hydrochlorothiazide in horses with hyperkalaemic periodic paralysis. *Res Vet Sci* 59:95–101.
38. Alberts MK. 2000. Pharmacokinetics of acetazolimide after intravenous and oral administration in horses. *Am J Vet Res* 61:965–8.
39. Tricarico D. 2004. Carbonic anhydrase inhibitors are specific openers of skeletal muscle BK channel of K^+-deficient rats. *FASEB J* 18: 760–1.
40. Toribio RE. 2004. Disorders of the endocrine system, In *Equine Internal Medicine*, 2nd Edition, edited by Reed, Bayley & Sellon, 1295–322, 1365–75. Philadelphia, PA: Elsevier.
41. Aguilera-Terejo E, Estepa JC, Lopez I, *et al*. 2000. Polycystic kidneys as a cause of chronic renal failure and secondary hypoparathyroidism. *Equine Vet J* 32:167–9.
42. Hudson NP, Church DB, Trevena J. 1999. Primary hypoparathyroidism in two horses. *Aust Vet J* 77(8): 504–8.
43. Baird JD. 1971. Lactation tetany (eclampsia) in a Shetland pony mare. *Aust Vet J* 47:402–4.
44. Beyer MJ, Freestone JF, Reimer JM, *et al*. 1997. Idiopathic hypocalcemia in foals. *J Vet Intern Med* 11:356–60.
45. Mansmann RA, Carlson GP, White NA, *et al*. 1974. Synchronous diaphragmatic flutter in horses. *J Am Vet Med Assoc* 165:265–70.
46. Richardson DW, Harrison LJ, Edwards GB. 1991. Two horses with hypocalcemia. *Vet Rec* 129(7):152.
47. Carlstedt F, Eriksson M, Kiiski R, *et al*. 2000. Hypocalcemia during porcine endotoxemic shock: effects of calcium administration. *Crit Care Med* 28:2909–14.
48. Zaloga GP. 2000. Ionized hypocalcemia during sepsis. *Crit Care Med* 28:266–8.
49. Laan TT, Spoorehberg JF, van der Kolk JH. 2000. Hypocalcemia in a four-week-old foal. *Tjidschr Diergeneeskd* 125(13):417.
50. Schoeb TR, Panciera RJ. 1978. Blister beelte poisoning in horses. *J Am Vet Med Assoc* 173:75–7.
51. Dart AJ, Snyder JR, Spier SJ, *et al*. 1992. Ionized calcium conentration in horses with surgically managed gastrointestinal disease: 147 cases (1988–1990). *J Am Vet Med Assoc* 201:1244–8.
52. Garcia-Lopez JM, Provost PJ, Rush JE, *et al*. 2001. Prevalence and prognostic importance of hypomagnesemia and hypocalcemia in horses that have colic surgey. *Am J Vet Res* 62:7–12.
53. Kaneps AJ, Knight AP, Bennett DG. 1980. Synchronous diaphragmatic flutter associated with electrolyte imbalances in a mare with colic. *Equine Pract* 2:18.
54. Freestone JF, Carlson GP, Harrold DR, *et al*. 1988. Influence of furosemide treatment on fluid and electrolyte imbalance in horses. *Am J Vet Res* 49:1899–1902.
55. Blood DC, Radostits OM, Henderson JA. 1983. Metabolic Diseases. In *Veterinary Medicine*, 6th Edition. 970–1014. London: Balliere Tindall.
56. Lorenz MD, Kornegay JN. 2004. Seizures, narcolepsy and cataplexy, In *Handbook of Veterinary Neurology*, 4th Edition, 323. Philadelphia, PA: Saunders.
57. Rosol TJ, Capen C. 1996. Pathophysiology of calcium, phosphorus, and magnesium metabolism in animals. *Vet Clin North Am Small Anim Pract*, 26:1155–84.
58. Rosol TJ, Capen C. 1997. Calcium-regulating hormones and diseases of abnormal mineral (calcium, phosphorus, magnesium) metabolism, In *Clinical biochemistry of domestic animals*, 5th Edition, edited by Kaneko JJ, Harvey JW, Bruss ML, San Diego CA: Academic Press.
59. Leicht E, Schmidt-Gayk H, Langer HJ, 1992. Hypomagnesemia induced hypocalcemia: concentrations of parathyroid hormone, prolactin and 1,25 dihydroxyvitamin D during magnesium replenishment, *Magnes Res*, 5:33–6.
60. Shah B, Santucci M, Finberg L, 1994. Magnesium deficiency as a cause of hypocalcemia in the CHARGE association, *Arch Paediatr Adolesc Med* 148:486–9.
61. Toribio RE, Kohn CW, Chew DJ, *et al*. 2001. Comparison of serum parathyroid hormone and ionized calcium and magnesium concentrations and fractional urinary clearance of calcium and phosphorus in healthy horses and horses with enterocolitis. *Am J Vet Res* 62:938–47.
62. Wijnberg ID, van der Kolk JH, Franssen H. 2002. Electromyographic changes of motor unit activity in horses with induced hypocalcemia and hypomagensemia. *Am J Vet Res* 63(6):849–56.
63. Hintz HF, Schryver HF. 1972. Magnesium metabolism in the horse. *J Anim Sci* 35: 755.

64. Hintz HF, Schryver HF. 1973. Magnesium, calcium and phosphorus metabolism in ponies fed varying levels of magnesium. *J Anim Sci* 37:927–30.
65. Wacker WE, Parisi AF. 1968. Magnesium metabolism. *N Eng J Med* 278:658–63.
66. Elin RJ. 1988. Magnesium metabolism in health and disease. *Dis Mon* 34:161–218.
67. White R, Hartzell H. 1989. Magnesium ions in cardiac function. *Biochem Pharmacol* 38:859–67.
68. Malpuech-Brugere C, Nowacki W, Rock E, *et al*. 1999. Enhanced tumour necrosis factor-alpha production following endotoxin challenge in rats is an early event during magnesium deficiency. *Acta Biochem Biophys* 1453:35–40.
69. Whang R. 1986. Magnesium and potassium interrelationships in cardiac arrhtythmias. *Magnesium* 5:127–33.
70. Tobey RC, Birnbaum GA, Allegra JA, *et al*. 1992. Successful resuscitation and neurologic recovery from refractory ventricular fibrillation after magnesium sulfate administration. *Ann Emerg Med* 21: 92–6.
71. Rook JAF, Storry JE. 1962. Magnesium in the nutrition of farm animals. *Nutr Abstr Rev* 32:1055.
72. Elin RJ. 1987. Assessment of magnesium status. *Clin Chem* 33:1695–970.
73. Harrington DD. 1974. Pathological features of magnesium deficiency in young horses fed purified rations. *Am J Vet Res* 35:503.
74. Meijer P. 1982. Two cases of tetany in the horse. *Tijdschr Diergeneeskd* 107:329–32.
75. Roden DM, Iansmith DH. 1987. Effects of low potassium and magnesium concentrations on isolated cardiac tissue. *Am J Med* 82:18–23.
76. Henninger RW, Horst J. 1997. Magnesium toxicosis in two horses. *J Am Vet Med Assoc* 211(1):82–5.

22
Cervical Vertebral Stenotic Myelopathy

Stephen Reed, Barrie Grant, and Yvette Nout

INTRODUCTION

Cervical vertebral stenotic myelopathy (CVSM) is a common cause of ataxia in horses and other animals. Early manuscripts describing this problem indicate one of the known risk factors for development of CVSM as genetic predisposition.[1] Further studies have shown that the problem is a developmental abnormality that may have genetic predisposition coupled with environmental influences. CVSM is characterized by ataxia and weakness, caused by narrowing of the cervical vertebral canal and compression of the spinal cord, often in combination with malalignment and malformation of the cervical vertebrae. Stenosis of the vertebral canal, anywhere from the first cervical vertebral body (C1) to the first thoracic vertebral body (T1), is the most important abnormality in CVSM.

Neurologic gait deficits in horses have been recognized since at least 1860,[2] and the term Wobblers syndrome was introduced in 1938 to describe several clinically observed abnormalities.[3] CVSM is the main cause of Wobblers syndrome and synonyms for CVSM include equine sensory ataxia, equine incoordination, and spinal ataxia.[4] As malformation, malarticulation, or malalignment of one or more cervical vertebral bodies generally leads to CVSM, the disease has also been referred to as cervical vertebral malformation (CVM) or cervical vertebral instability (CVI). At present, CVSM seems to be the most appropriate term.

CVSM is the leading cause of non-infectious spinal cord ataxia in the horse[5–8] and is estimated to affect 2% of Thoroughbred horses[9] but has been identified in many breeds including Arabians, Morgans, Appaloosas, as well as Thoroughbreds.[10–12] Congenital anomalies and malformations of the vertebral column that could lead to compression of the cervical spinal cord are reported infrequently, including occipitoatlantoaxial malformation (OAAM).[12] Other types of malformation do exist and reports have been published on butterfly vertebrae, hemivertebrae, and block vertebrae as well as on atlantoaxial subluxation and atlantoaxial instability.[12] Spinal cord compression may also result from traumatic injury,[13] vertebral fracture,[14–16] vertebral neoplasia,[17] discospondylitis,[18,19] diskospondylosis,[20] intervertebral disk protrusion,[18,21] and arachnoid diverticulum.[22]

Important differential diagnoses for spinal ataxia in a young horse include CVSM, equine protozoal myeloencephalitis (EPM), trauma, equine degenerative myeloencephalopathy (EDM), and equine herpesvirus 1 myeloencephalopathy (EHV-1). Other less common causes of ataxia and weakness result from neurologic diseases such as rabies, botulism, encephalitidies (Eastern, Western, Venezuelan, and West Nile), brain abscesses, trauma, neoplasia, and hepatoencephalopathy. Whenever possible, it is important to be certain of one's diagnosis prior to initiation of treatment. Surgical management of horses that have been diagnosed with spinal cord compression involves the use of a ventral stabilization procedure. The surgical technique was initially described in 1979 and in the hands of some surgeons is now considered a routine procedure. Based upon the experience of the authors, owners and veterinarians can expect clinical improvement in approximately 80% of the horses on which it is used.[23] Although clinical improvement may be somewhat variable, approximately 63% of the horses return to athletic function and another 15% are suitable for breeding.

About 10% have poor response to treatment and may be turned out and live a relatively normal life at pasture, while failure to improve can be expected in another 12% of the patients.[23]

TYPES OF CERVICAL VERTEBRAL STENOTIC MYELOPATHY

Rooney distinguished 3 types of CVSM.[9] In type I, the vertebral column is fixed in flexed position at the site of malarticulation/malformation, which generally occurs at C2–C3 but has been observed at other sites as well. Type I CVSM is uncommon and often present at birth. In type II CVSM, symmetrical overgrowth of the articular processes causes spinal cord compression during flexion of the neck. Type II lesions occur most often in sucklings and weanlings and are generally found in the mid-cervical region. Type III CVSM is characterized by asymmetrical overgrowth of one articular process that leads to compression of the spinal cord either directly by the bony proliferation or indirectly by the associated soft tissue hypertrophy. Type III is most often seen in mature horses but may begin as early as 1 to 3 years of age. This lesion most often affects C5–C6 and C6–C7.[24] The authors' recent publications divide CVSM into 2 broad categories or classes of horses; one affecting young horses with compression as a result of developmental abnormalities of the cervical vertebral column, while the second affects older horses. The condition of young horses is observed most often in Thoroughbreds and is a multifactorial disease including such factors as gender, inheritance, diet, trauma, and rate of growth.[6,25] The second group or class of horses affected are older horses (young adults to old age) of all breeds with osteoarthritic changes of the articular processes. In all categories, the cause of the stenosis is related to morphological changes of the cervical vertebrae, which in young horses (foals and yearlings) are related to malformation of the vertebral canal, enlargement of the physes, extension of the dorsal aspect of the vertebral arch, angulation sometimes with fixation between adjacent vertebrae, and malformation of the articular processes as a result of osteochondrosis.[26] In older horses, changes often include malformation with degenerative joint disease of the articular processes, wedging of the vertebral canal, periarticular proliferation with or without a synovial or epidural cyst and overt fractures of the articular processes.[26,27] It is important to note that many older horses will have bony abnormalities of the cervical vertebral column; however, only a small percentage of horses develop clinical signs as a result of spinal cord compression.[28]

The diagnosis of CVSM is based upon the presence of clinical signs of symmetric spinal ataxia, narrow cervical vertebrae on radiographs, and contrast myelography along with elimination of other possible causes of spinal ataxia. The *gold standard* for confirmation of the diagnosis remains a postmortem examination.[6,24]

Cervical static stenosis is defined as the narrowing of the vertebral canal with subsequent compression of the spinal cord during myelography, regardless of the position of the neck. Although spinal cord compression is noticeable in neutral views, extension of the neck may exacerbate this compression suggesting a degree of coexisting dynamic instability and compression. The most common sites for static stenosis are at C5–C6 and C6–C7.[6,24,29] Narrowing of the cervical vertebral canal can occur at any site within the vertebral column and stenosis at more than one site is common.[5,6,10,27]

CLINICAL SIGNS

CVSM is most frequently seen in young, well-fed, rapidly growing horses of all breeds, although this condition appears more often in Thoroughbreds, suggesting an inherited component that has been reported in many breeds.[6,10] The age at presentation to a veterinarian is usually between 1 and 2 years; however, the age at onset is often much earlier because of the developmental factors involved in the pathogenesis of the stenosis. Onset of clinical signs is dependent upon the degree of compression or repeated trauma to the spinal cord. In most horses the onset is early in life; however, it can be at a much older age, especially in horses with arthritis of the vertebral processes, which often involves the articular processes of the caudal cervical vertebrae. CVSM has been reported to be more common in male horses.[5,6,7,10,24,30]

Although a common historical finding is acute onset of ataxia or gait abnormalities following trauma, such as, a fall or halter-breaking accidents, in many cases the horse will have been mildly ataxic prior to the observed trauma. In fact, the mild neurologic deficits may have been the cause of the traumatic incident that results in exacerbation of the neurologic signs. Other historical findings are that the horse is growing rapidly or has recently gained a

lot of weight or that the affected foal is out of a high-milk producing mare and is large for its age. In other cases, the onset may be more insidious and weeks or months may pass before neurologic deficits are noticed. Static stenosis, usually as a result of osteoarthritis of the articular processes, is observed in horses four years of age and older.

Physical examination may reveal abrasions around the heels and medial aspect of the thoracic limbs due to interference and short, squared hooves due to excessive toe-dragging. Although the physical examination is often unremarkable, many young horses affected with CVSM have signs of developmental orthopedic disease such as physitis or physeal enlargement of the long bones, joint effusion secondary to osteochondrosis, and flexural limb deformities. Stewart *et al.* demonstrated the increased incidence of osteochondrosis in horses with CVSM.[31] Evidence of gray matter and spinal nerve root damage such as cervical pain, atrophy of cervical musculature, and cutaneous hypalgesia adjacent to affected cervical vertebrae is rare in young horses. These signs are more common in older horses with arthropathies of the caudal cervical vertebrae and may demonstrate focal muscle wasting, focal sweating, or palpable bony abnormalities of the vertebral articular processes.

Complete neurologic examination is described elsewhere in this text (Section 2, Chapter 5) but in general there is normal cranial nerve function and cervical reflexes. The thoracolaryngeal reflex, which is the adductory movement of the arytenoid cartilages of the larynx in response to a slap on the thorax (slap test), may be diminished in horses with cervical spinal cord disease. A negative result for this test does not exclude the possibility of cervical spinal cord disease, however.[32]

Neurologic examination will reveal upper motor neuron signs and general proprioceptive deficits compatible with symmetric compression and damage of the cervical spinal cord white matter. Symmetric ataxia, paresis, dysmetria, and spasticity will be present in all four limbs, usually more noticeable in the pelvic limbs than in the thoracic limbs. In horses with significant degenerative joint disease of the articular processes, lateral compression of the spinal cord may lead to asymmetry of the clinical signs.[8] Ataxia and spasticity, followed by weakness, is usually observed in the pelvic limbs first and then progresses to the thoracic limbs.[10,33] In a standing horse, conscious proprioceptive deficits may be present such as an abnormal wide-based stance, abnormal limb placement, and delayed positioning reflexes. Ataxia and paresis can be noted when the horse walks during which it may demonstrate truncal sway, circumduction of the hindlimbs, toe-dragging, and stumbling. These signs will be exacerbated when the horse is circled, led up and down a hill or over obstacles, or when the horse's head is elevated during the neurologic examination. The horse may exhibit an exaggerated, stiff-legged movement, which is most likely a result of simultaneous dysmetria and spasticity. In young horses, clinical signs of ataxia often progress and then stabilize. This cycle of progression followed by stabilization may occur several times prior to final confirmation of the diagnosis using radiography and myelography.

NEUROPATHOPHYSIOLOGY

The characteristic signs of spinal cord compression due to CVSM are a result of lesions in the white matter of the cervical spinal cord. Clinical signs are characterized by symmetric ataxia as a result of damage to the ascending general proprioception pathways (ataxia) and descending upper motor neuron pathways (paresis).[4] Progression of disease is due to prolonged compression or repeated trauma to the spinal cord, with initial damage to the white matter followed by gradual spread to the deeper areas. The lateral funiculi are especially susceptible to degeneration by pressure or compression. Controversy exists regarding the presence of altered blood supply to the spinal cord and its potential role in the pathogenesis of CVSM.[10]

A cervical spinal cord compressive lesion produces more severe pelvic limb than thoracic limb ataxia because of the more superficial anatomic location of the proprioceptive tracts from the pelvic limbs, the dorsal spinocerebellar tracts, compared with that of the thoracic limbs, the rostral spinocerebellar tracts.[4,34] Disparity in signs between the pelvic and thoracic limbs may also be explained by the greater distance of the pelvic limbs from the center of gravity of the horse and the greater percentage upper motor neuron synapses in the gray matter of the cervical intumescence.[4] Obvious signs of disturbance of the ascending general somatic afferent pathway, characterized by decreased pain sensation, occur rarely.

DIAGNOSIS

A presumptive clinical diagnosis is obtained by a combination of a detailed history from the owners or trainers, the signalment of the animal, and the recognition of ataxia with a neuroanatomical localization caudal to the foramen magnum on a neurologic examination. Hematologic and serum biochemical parameters are generally unremarkable in horses with CVSM. Cerebrospinal fluid (CSF) analysis is normal in the majority of cases, but CSF analysis remains an important ancillary diagnostic tool in the evaluation of equine neurologic disorders. CSF collected from horses with CVSM is generally within normal limits.[35] Xanthochromia, subtle elevation of the white blood cell count, and a rare increase in aspartate transaminase activity are other changes that can be demonstrated in CSF from horses with CVSM.[10] Examination of (cerebrospinal fluid-creatine kinase) CSF-CK activity had been thought to be a useful diagnostic test for horses with CVSM; however, in horses with compressive disease, an increase of CK is uncommon, presumably because the rate of release of CK is too slow to allow accumulation of the enzyme.[36] CSF electrophoresis can be used as an aid to diagnose cervical compression. Furr *et al.* demonstrated that CSF high-resolution electrophoresis revealed a less prominent β_2-globulin fraction and more frequent post-β peaks in horses with compressive disease when compared to horses without neurologic disease.[37]

Lateral radiographs of the cervical vertebrae, obtained in the standing horse, should reveal bony malformations of the cervical vertebrae. The five characteristic bony malformations of the cervical vertebrae in horses with CVSM are *flare* of the caudal vertebral epiphysis of the vertebral body, abnormal ossification of the articular processes, malalignment between adjacent vertebrae, extension of the dorsal laminae, and degenerative joint disease of the articular processes.[5,6,7,9,10,12] Degenerative joint disease characterized by osteochondrosis and/or osteoarthrosis of the articular processes is a common lesion identified on cervical vertebral radiographs in horses affected with CVSM.[6,27] Subjective assessment of cervical radiographs may not adequately discriminate between horses with and without CVSM, however.[7] Also compressive lesions can develop at vertebral sites that are not affected by bony malformation.[10,31]

Minimum sagittal diameter (MSD) values were published for horses under anesthesia,[10] however, magnification made these values impossible to interpret and unreliable in cervical vertebral radiographs obtained in standing horses. Subsequently, a non-invasive, semi-quantitative, radiographic CVSM scoring system was developed in which multiple radiographic characteristics were considered, one of which was stenosis of the vertebral canal. The presence of stenosis was assessed by the corrected MSD (ratio of MSD to vertebral body length) in which the MSD was measured either intra-vertebral or inter-vertebral.[26,27] (Figure 22.1, Table 22.1)

An intra-vertebral ratio method of canal diameter assessment was developed in humans[38] that improved the accuracy of diagnosis of cervical spinal stenosis, and a similar protocol has been developed for use in adult horses.[27] It is essential that direct lateral radiographs are obtained in order to use this method. The sagittal ratio is the ratio of the MSD to the sagittal height of the maximum dimension of the cranial aspect of the vertebral body. Assessment of this ratio is independent of radiographic magnification. A ratio of less than 50% at C4, C5, or C6 or a ratio of less than 52% at C7 is associated with a high likelihood (likelihood ratio—26.1:41.5) of having cervical stenotic myelopathy. The sensitivity and specificity of this ratio method is >89% at each vertebral site.[27] Including inter-vertebral MSD measurements for assessing canal width may increase the sensitivity of using standing survey radiographs to diagnose CVSM.[20,39] In foals, Mayhew's scoring system[26] appeared to predict the development of CVSM accurately, but the sagittal ratio method[27] was developed in adult horses and it has not been investigated whether the cut-off values are valid to use in horses less than 1 year of age. The sagittal ratio method is accurate for identification of stenosis of the cervical vertebral canal; however, the use of this method to identify specific sites of spinal cord compression will result in false positive diagnoses.[27,33] Therefore, myelography remains the diagnostic tool of choice for antemortem diagnosis of CVSM and location of specific sites of compression (Figure 22.2).

Myelography is required to confirm diagnosis of focal spinal cord compression and to identify the location and number of lesions, particularly if surgical treatment is to be considered or pursued.[5,24,27,40] The techniques for performing a myelogram has been



Figure 22.1. Survey radiograph of the third and fourth cervical vertebrae. The intra-vertebral sagittal ratio (A:B) is determined by A (minimum sagittal diameter) and B (sagittal height of the maximum dimension of the cranial aspect of the vertebral body). The inter-vertebral sagittal ratio is shown as C:B.

Table 22.1. Cervical Vertebral Sagittal Ratio Measurements Given with the Proportion Horses Affected with CVSM and the Likelihood Ratios. Data from Rush Moore *et al.*[27]

	C4	C5	C6	C7
Sagittal ratio (%)	<50	<50	<50	<52
Proportion affected* (%)	86 (30/35)	78 (29/37)	83 (34/41)	82 (27/33)
Likelihood ratio	28.6	26.1	41.5	39.0

*Percentage of horses affected with CVSM that had sagittal ratios less than 50–52% at the site of compression.

described using a non-ionic, water-soluble contrast agent (iopamidol, iohexol). The contrast is administered through the atlanto-occipital space into the subarachnoid space after withdrawal of an equal volume of CSF.[35,40] Radiographs are taken in neutral, flexed, and extended positions of the neck. Criteria for evaluating equine myelographic radiographs are established but continue to be the source of some debate. Criteria that have been reported or are used include a reduction of thickness of the contrast columns to less than 2 millimeters[40] and attenuation of both the dorsal and ventral contrast columns by greater than 50% at diametrically apposed sites.[7] Currently, complete attenuation of the ventral contrast column with 50% attenuation of the dorsal contrast column is used as myelographic evidence of compression.[41] However, the accuracy of this criterion has recently been questioned, and use of the minimal sagittal dural diameter (MSDD), which is the average sagittal diameter of the dural space measured inter-vertebrally, has been advocated to precisely define the sites of spinal cord compression (Figures 22.3–22.6, Table 22.2).[33,39,42]

Contrast-enhanced computed tomography (CECT) is considered to be more useful than myelographic radiography to diagnose and characterize vertebral stenosis in humans and has been evaluated in the horse.[8] In a postmortem study involving 6 horses with CVSM, CECT images could be obtained from C1–T1. CVSM lesions were accurately detected and significant additional information, regarding location and severity of the lesion, was obtained.[8] The main indications for CECT are pre-surgical evaluation of



Figure 22.2. Myelogram demonstrating compression of the cervical spinal cord at C4–C5. Measurements of the dorsal contrast column, the ventral contrast column, and the sagittal dural diameter are given (Table 22.2). The dorsal contrast column reduction is 67% and the sagittal dural diameter reduction is 45%.

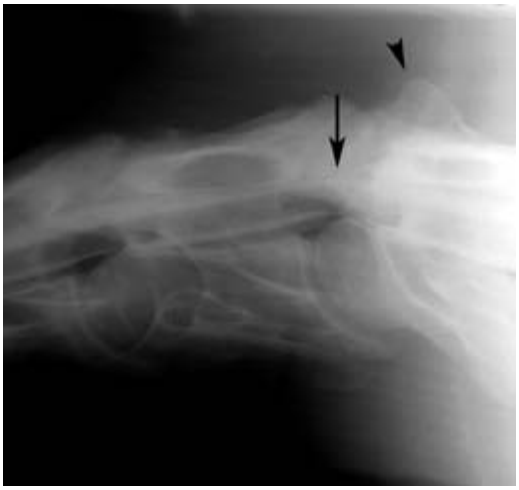


Figure 22.3. Myelogram of the caudal cervical vertebrae demonstrating severe osteoarthritis of the articular processes of C6–C7 (A). These arthritic changes may lead to compression of the spinal cord as demonstrated here.

the cervical vertebral column and spinal cord at sites that are suspected to have dynamic compressive lesions and evaluation of lateral compressive lesions in horses strongly suspected to have CVSM without myelographic evidence. Depending on the patient aperture and table size, evaluation of C1–C7 is possible with CECT.

POSTMORTEM AND HISTOPATHOLOGY

On gross examination of the vertebral column, bony abnormalities and malformations such as those detected by radiography may be present. Narrowing of the vertebral canal frequently occurs through soft tissue swelling and proliferation or through thickening of the ligaments between the vertebral bodies, and particularly of the lateral ligamentum flavum.[30,43,44] The presence of cysts and bony proliferations also leads to compression of the spinal cord. Changes in the ligament and the development of cysts are often associated with degenerative changes in the articulations of the vertebral bodies.[44] Abnormal biomechanical forces or instability of articulations result in stretching and tearing of the ligamentum flavum and joint capsule with subsequent fibrovascular and fibrocartilaginous proliferation, osteosclerosis of the dorsal lamina, and osteophyte formation on the articular processes.[6] Horses with CVSM have decreased differentiation of cartilage and osteopetrosis, sometimes associated with osteonecrosis and osteoclasia in the cervical vertebrae. Similar lesions may be present in the costochondral junctions and seem to be associated with osteochondrosis dissecans.[10]

On gross evaluation of the spinal cord, lesions may[45] or may not[46] be detected. The characteristic finding is a focal pressure–induced lesion in the cervical spinal cord, affecting the gray and, especially, the white matter when examined microscopically.[10] A pressure-induced lesion may be identified by recognizing flattening of the fixed spinal cord in a transverse section, when compared to adjacent segments or a decrease in height of the spinal cord.

At the level of compression, prominent features of the focal lesion include neuronal fiber swelling and degeneration, occasional spheroids, astrocytic gliosis, increased macrophage activity, and increased perivascular collagen. Myelin degeneration or loss was reported to be greatest in the ventral and lateral funiculi.[45] Vessels at the site of a primary lesion may also be surrounded by increased collagen indicating a process of fibrosis.[10] In more severe cases,

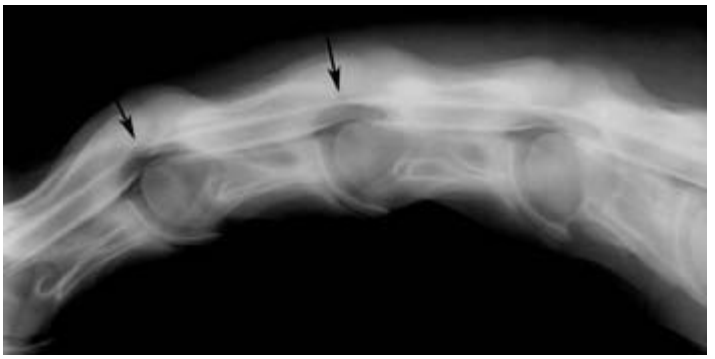


Figure 22.4. Cervical myelogram demonstrating dynamic compression of the cervical spinal cord at C4–C5 (2 arrows). The compression is not noticeable on the neutral view however, becomes obvious when the head and neck are flexed as in this view.



Figure 22.5. Cervical myelogram demonstrating static compression of the cervical spinal cord at C6–C7.

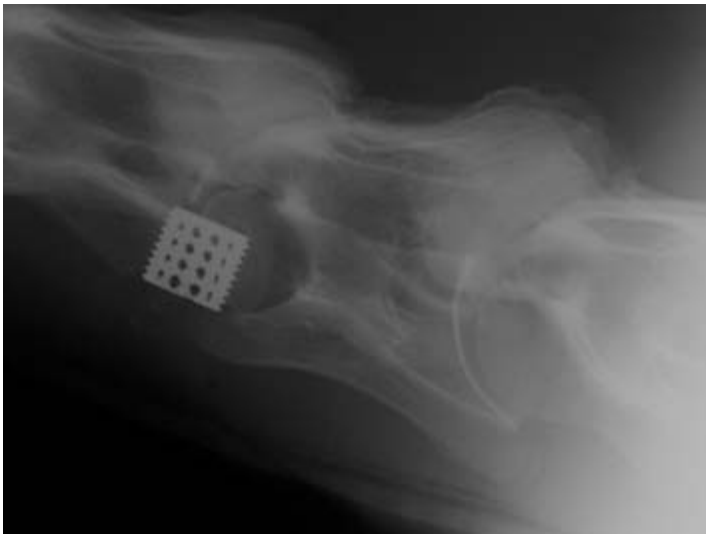


Figure 22.6. Lateral survey radiograph of the cervical vertebrae demonstrating placement of a threaded Bagby basket during ventral stabilization surgery. Although placement is not ideal, adequate fusion and clinical improvement resulted.

Table 22.2. Measurements of the Dorsal Contrast Column, the Ventral Contrast Column, and the Sagittal Dural Diameter for the Myelogram Shown in Figure 22.2

Line	Dorsal CC (mm)	Ventral CC (mm)	SDD (mm)
A	7	5	22
B (inter-vertebral)	3	0	12
C	7	5	22

CC, contrast column; SDD, sagittal dural diameter.

vacuolated spongy degeneration of the white matter may be seen.[46] Proximal and distal segments and stumps of injured axons swell and may resemble spheroids that are characteristically seen in EDM. However, the spheroids in EDM are found primarily in the gray matter, whereas the spheroids in CVSM are more commonly found in the white matter.[10]

Fiber degeneration or Wallerian-like neuronal fiber degeneration may be present, related to, but distant from the focal lesion. The secondary neuronal fiber degeneration is characterized by a loss of myelin and axons that occur. In areas of marked fiber degeneration, perivascular fibrosis in the white matter is often evident. Astrocytic gliosis is a prominent and persistent finding in areas of neuronal degeneration in horses with chronic CVSM.[47] The characteristic pattern of fiber degeneration, with developing gliosis in ascending white matter tracts above and descending tracts below the primary lesion, can be used to map the site of an undetected primary lesion and allow further sections to be examined until the primary lesion is detected.

The relative roles of direct injury to nervous tissue and alterations in spinal cord blood supply are not clearly defined in CVSM. Return of function following a partial focal compressive myelopathy has not been shown to be dependent on remyelination of those axons that remain intact and may be due to adaptation of remaining nervous tissue.

TREATMENT

Medical Treatment

Medical therapy in horses with CVSM is aimed at reducing cell swelling and edema formation with subsequent reduction of the compression on the spinal cord. In the immediate period following an acute onset of neurologic disease, treatment with anti-inflammatory medications is indicated. Treatment with anti-inflammatory drugs, such as non-steroidal, anti-inflammatory drugs and dimethyl sulfoxide, is most commonly provided. Choice of medical treatment of CVSM depends in part on type of lesion, severity of clinical signs, age of the horse, and other factors.

For horses less than one year of age, changes in management may influence the development of CVSM. These include restricted exercise and diet, along with alterations in the concentrations of trace nutrients such as copper and zinc in the diet. The *paced growth* program, of which the efficacy has been demonstrated in young horses with early clinical or radiographic signs of CVSM,[48] includes stall rest and a diet that is aimed at reducing protein and carbohydrate intake and, thus, reducing growth rate allowing the vertebral canal to "catch up". It is important that the diet chosen, should meet minimum requirements of essential nutrients, and during the period of growth retardation, the selected individuals should be under careful nutritional supervision.[49] In young horses, supplementation with vitamin E/selenium is recommended as EDM is an important differential diagnosis that may improve following vitamin E administration.[50]

In adult horses with compressive lesions of the spinal cord, the options for medical therapy are restricted to stabilizing a horse with acute neurologic deterioration and injecting the articular joints with a combination of corticosteroids, antimicrobials, and chemical mucopolysaccharides such as hyaluronate sodium in an attempt to reduce soft tissue swelling and stabilize or prevent further bony proliferation.[51,52] Injecting articular joints is most beneficial in horses that demonstrate zero or only minimal neurologic deficits (grade 0–2) and that have moderate to significant degenerative joint changes noticeable on radiographs of the cervical vertebral column. Horses that fit into this last category are generally older horses (>5 years) that are under training and have developed osteoarthritic changes, usually in the caudal cervical vertebral joints.

Surgical Treatment

Indications for surgery are described throughout this chapter but are briefly repeated here. The best surgical candidates are young horses with only

one or two myelographic lesions and with mild to moderate clinical signs and no evidence of concurrent disease. It is also important for the owner to have realistic expectations and to be aware that the final determination of the results may not be fully known for as long as one year. Horses suffering from neurological disease including CVSM and that are insured present an additional set of issues for the owner and the veterinarian. In the authors' opinion, there are several important insurance aspects for consideration. The most common questions encountered are: what constitutes a horse that is a candidate for medical or surgical correction and when does a horse become a candidate for humane destruction. The response to the first question is impacted by several factors including the severity of clinical signs, the number of sites affected, the owners' commitment to the horse, and the economic value of the horse combined with the cost for performing surgery. In most cases, the owners have two very important criteria which they request from the veterinarian. The first is for a realistic prognosis for the horse in relation to their intended use (i.e., racing, showing, breeding, etc), and the second is a reasonable estimate of the monetary cost for the surgery and hospitalization as well as the rehabilitation and training time. This information can then be forwarded to the insurance company to discuss the coverage available.

When a horse is a candidate for humane destruction is governed by the guidelines established by the AAEP Insurance committee on behalf of the American Association of Equine Practitioners (AAEP). Important criteria include: whether the horse is suffering inhumanely, will it require pain-relieving medication for the remainder of its life, is the condition chronic and incurable, and is the animal a danger to itself, other animals, and its handlers. Beyond these guidelines, the owner is the most important person determining whether the horse is a candidate for humane destruction. Some insurance underwriters have established a *wobbler clause* which, in general, says that for a horse with CVSM to be a candidate for humane destruction, it must be at least a grade 3 out of 5 in severity of clinical signs and have a myelographic confirmation of a surgical lesion. This statement is a generality and in no way do the authors intend to interpret the policy guidelines of any insurance underwriter or company. Another common question the authors are often asked is about the safety of handling a horse with a neurological disease, in particular CVSM. In the authors' opinion, it is important for everyone dealing with the patient to be aware of what signs a horse with neurological disease might show and then to notify all potential handlers and caregivers of the horse. In most cases, the horse with neurological gait deficits less than a grade 4 can be managed in a fashion similar to other horses. A horse with grade 4 neurologic gait deficits may fall with normal movements and therefore needs to be handled very carefully. In response to the question of liability, it is the authors' opinion that the owner has the ultimate responsibility for the horse and therefore assumes the lions share of the liability. However, with more than 30 years of managing horses with neurological disease of varying severity, we are unaware of any instance in which an owner or handler has been injured as a result of managing an affected horse. Notwithstanding this, it is very important that the owners be aware of their responsibility to notify all potential handlers and/or riders of the horse informing them of the primary problem as well as telling them what impact the problem may have on the horse's ability to be exercised.

SURGICAL TECHNIQUE

There have been a number of technical changes since the adaptation of the Cloward technique (anterior interbody fusion) and was first described as a treatment for cervical vertebral malformation.[53] The Cloward technique utilized the principle of dynamic compression that results from having a circular bone dowel hammered into a slightly smaller diameter hole drilled between adjacent vertebra that need to be stabilized. The next significant modification was the use of a stainless steel circular implant that had numerous holes to allow for the cancellous bone from the drilling procedure to be used as an autologous graft resulting in an osseous fusion.[54] This technique was used for over two decades with great success, although there was occasional implant migration and an increased incidence of postoperative vertebral fractures from the forcing of the oversized implant into the pathological bone.

The use of the threaded BAK implant for the stabilization of lumbar vertebra in humans led to the development of the Seattle Slew implant in 2000. This technique uses a partially or fully threaded cylinder that is screwed into a previously drilled and

threaded implant site. The implant site is prepared using a Kerf cleaning instrument so that a peninsula of bone is left that will accelerate fusion.

Ideally, the procedure needs to be done in a surgical facility that is separate from the room were other equine orthopedic procedures are performed. A method of getting an anesthetized patient on a table into dorsal recumbency with the cervical area placed in a cervical brace is required. Good lighting, reliable aspiration, positive pressure anesthesia with blood pressure and cardiac monitoring, and intraoperative imaging (C-arm or digital films) are all necessary for performing this procedure. The use of the Seattle Slew implant requires a number of specifically designed instruments that are commercially available. In addition, a general instrument pack for standard opening and closing, large curved osteotome, orthopedic hammer, depth gauge, Deaver and Inge retractors, aspiration tips and hoses, orthopedic reamers with nitrogen hoses and tank and regulators and large roungers are all necessary. The use of a Hall drill to prepare and remove the excessive intervertebral disc is also recommended.

Prior to performing the surgical procedure, a preoperative endoscopic exam is performed to determine that there is no recurrent laryngeal nerve dysfunction. If present, the approach to the vertebral body should be on the dysfunctional side of the trachea, that is, left side if a left sided paralysis—to prevent damage to the normal nerve during the retraction process. Failure to do so might result in a bilateral laryngeal paralysis that could seriously compromise the horse's airway and recovery from anesthesia.

Preoperative antibiotics are administered that are standard for the surgical facility. Non-steroidal, anti-inflammatory drugs are also administered preoperatively unless anesthesia dictates they be withheld until after the completion of the procedure. Corticosteroids are only administered to the very ataxic patients (>3.5/5 grade). Routine preoperative preparation such as screening clinicopathologic evaluations and tetanus toxoid are recommended. Clipping and a preliminary cleaning of the ventral cervical area before anesthesia will assist in reducing anesthesia time. After induction and intubation, the patient is placed in dorsal recumbency on a well-padded surgical table. The cervical area is placed in a cervical brace that is designed to hold an intraoperative radiology plate. After standard clipping, shaving, and skin preparation, the level of the cervical vertebrae that are to be fused are located by obtaining a preoperative image after 14-gauge needles have been placed subcutaneously over the vertebral bodies. In mature horses, the vertebral bodies are approximately a hand's width apart. Care should be taken to have the needles on the cassette side of the cervical area to reduce any parallax problem. The second cervical vertebra needs to be included so the characteristic formation of C2 can be used as a reference. Standard toweling and draping technique is utilized as for any sterile procedure. Small towel clamps are used to mark the position of the placement needles to prevent any confusion that palpation of needles through the towels and drapes may cause, which could result in selection of the wrong site.

A 20-cm incision is made on the ventral midline centered over the previously identified intervertebral area that is to be fused. The ventral cervical subcutaneous muscle is also incised down to the sternothyrohyoideus muscles. The thickness of these muscles is quite variable depending on the patient's age and degree of neurological deficits. The fascia is separated from the side of the trachea with blunt finger and scissor dissection deeper to the carotid trunk. The recurrent laryngeal nerve and vagosympathetic trunk are identified so they can be protected from excessive trauma during the retraction process. Using large hand-held retractors, the trachea and sternocephalicus muscles are separated to expose the ventral aspect of the vertebral bodies. The longus colli muscle overlies the vertebral bodies, but usually the ventral spine of the anterior body can be palpated through the muscle (except for C6 that has a ventral spine so small that palpation is not possible.) A 4-cm incision is made over the ventral spine parallel with the muscle fiber down to the spine. The muscle insertion on the spine is elevated with a large blunt elevator (a sharp osteotome can be used, but the possibility of injury to the esophagus is increased). The spine is isolated using two pairs of Inge retractors. The spine is removed using a large curved osteotome and orthopedic hammer down to the level of the intervertebral disc appearing on the anterior aspect of the posterior vertebra. At this time, a small exploratory hole is drilled with a 16-mm drill through a matching drill guide that has been placed with the posterior edge of the drill guide on the epiphyseal scar of the anterior vertebra (a distinct white undulating line in

young and middle age patients). The test hole is drilled to a depth of 8 to 10 mm and the bone removed. The very white intervertebral disc should now be visible. Two to three marker pins are then placed through a marker pin guide to assist in drilling the implant hole with the disc in the center of the hole. An intraoperative image is obtained, and the marker pin with the most ideal location is selected. If there is no ideal placement, then repeating this procedure is recommended. After the correct pin placement site has been determined, the pin guide and the other pins are removed. This pin will then be placed into the center hole of the guide bar to assist in placing the large drill guide in the correct location. The drill guide is secured in place by the use of an orthopedic hammer and impacter. The implant site is then prepared by using a series of thin core saw, thick core saw, large pointed drill, and large flat drill. The depth of each should be set to 20 mm by premeasuring the set rings on the drill guide. Then the #1 Kerf cleaner is placed into the drill guide and the Kerf is started. The drill guide is then removed, and the tap is used to countersink the leading aspect of the implant site to allow for the use of the 1 mm larger #2 Kerf cleaner. The Kerf cleaner is then drilled by hand to a depth of 25 to 30 mm (there are guide lines on the Kerf cleaner set at 10 mm increments), and an intraoperative image is obtained with the #2 Kerf cleaner in place to determine the correct depth. Ideally, the depth should not be any closer than 10 mm from the spinal canal to reduce any fractures from a violent recovery. After the depth has been determined, the site is tapped and the threaded implant is twisted into place with an inserter until it is very secure. A partially threaded implant is used, but if it does not become secure, a fully threaded implant is used to provide a more secure implant. Care must be exercised when using a fully threaded implant as the design allows for it to be self tapping and it could be possible to twist it all the way to the spinal canal.

After the implant placement has been confirmed with another image, the harvested bone graft (obtained by saving the drilling debris on a sterile sponge that has been soaked with blood) is firmly placed into and over the implant. The longus colli muscle is then reapposed by using a 2-layer closure with 0 PDS. The surgery site is then examined for any foreign debris and thoroughly flushed. The ventral cervical muscles are then reapposed in a 2-layer closure with 0 PDS in a simple continuous pattern. Skin staples are used on the skin. Recovery from anesthesia can usually follow routine procedures, although a determination about how well the horse will recover or whether it might need special assistance can be determined by the way it recovered following its myelogram.

The modifications of the procedures have resulted in reduction in surgery time, better bony fusion, less pain, and improved outcome for the horse. Since the inception of the modern procedure, more than 2,000 horses have benefited from use of these procedures, and long-term survival appears to be greater than 80%, although this has never been critically reviewed and published. The aim of surgical treatment is to stop the repetitive trauma to the spinal cord, which is caused by narrowing of the vertebral canal, and thereby allow the inflammation in and around the spinal cord to resolve. Restoration of an adequate blood supply to the spinal cord is vital to reduction of edema and removal of inflammatory mediators from the affected site.

Because the procedure has been in use for more than 25 years, surgical treatment of CVSM has become less controversial, although several important concerns remain such as the cost, the duration of the recovery period, which can be up to one year, safety of the horse after surgery, and the potential heritability of the vertebral canal stenosis. Concerns regarding safety of the horse following surgery are based on the assumption that neurons do not regenerate completely following vertebral body stabilization, and thus even if the compression is alleviated, the irreversible neuronal damage that is present could make a horse unsuitable for performance activities. In humans, 80% of patients with cervical spondylotic myelopathy that had cervical laminectomy with posterior lateral mass fusion/fixation showed improvement,[55] and 80–90% of humans with dyscogenic radiculopathy of the cervical spine showed improvement following anterior interbody fusion.[56] In dogs with caudal cervical spondylomyelopathy, 89% showed improvement after surgical intervention,[57] and 77% of horses with CVSM showed improvement of neurologic deficits and 46% returned to performance activity.[25] This suggests that surgical intervention appears beneficial in humans, dogs, and horses, and that safety for performance should be evaluated on a case-by-case basis by performance of thorough neurologic examinations.

In some of the early literature describing the surgical techniques for CVSM, a subtotal dorsal decompression laminectomy was described. In this procedure, the caudal aspect of the vertebral arch of the cranial vertebrae and the cranial aspect of the vertebral arch of the caudal vertebrae are removed.[52,58] This surgery offers almost immediate decompression of the spinal cord; however, the technique is technically demanding and carries a high risk of serious complications.

Following interbody fusion surgery, an improvement of 1–2 out of 5 grades is expected. Because of the low probability that a horse improves more than 3 out of 5 grades, we recommend surgery in horses that are at most moderately ataxic (grade 3 out of 5) and that are compressed at a maximum of 2 sites.

Adult horses undergoing ventral stabilization that are western blot positive for antibodies against EPM on CSF should receive treatment for EPM during hospitalization. This recommendation is based on the fact that in stressed situations, clinical signs associated with EPM may be exacerbated. This may lead to deterioration in the horse's condition immediately, postoperatively, and in a delayed onset of improvement of clinical signs.

PROGNOSIS

Whether horses are not treated, medically treated, or surgically treated, the response and the prognosis depend largely on the age of the horse, the severity of the neurologic deficits the horse demonstrated at the time of examination, the duration of neurologic signs, and the expected level of performance. Generally, a horse with CVSM will be able to live, however performance may be impaired. This is of concern when horses are insured. Depending on the policies issued, mortality claims may or may not be granted. It is uncommon but not unprecedented for insurance agencies to take over ownership of the affected horse and salvage it for athletic or breeding purposes. Severely affected animals and affected animals in which treatment is not an option or not effective are generally humanely destroyed.

Without treatment, the prognosis in all types of CVSM is poor to be guarded, as there is continued damage to the cervical spinal cord with an increasing chance of severe cord destruction following trauma. The initial response to medical therapy with anti-inflammatory drugs in cases of acute spinal cord damage is generally good; however, if bony malformations or soft tissue proliferations exist, neurologic deficits will remain present. Articular joint injections with corticosteroids often result in reduced soft tissue swelling in horses with significant arthropathies;[51,52] however, these injections generally need to be repeated at variable intervals. Again, the prognosis depends upon the severity of neurologic deficits and the severity of the degenerative joint changes.

The clinical response to ventral stabilization depends on the ability to detect all compressed sites and the accuracy of the diagnosis. In humans, factors associated with a poor outcome following surgery include a poor initial clinical condition and a longer duration of symptoms.[55] Optimal outcomes are achieved if surgical intervention is pursued shortly after the first clinical signs.

PATHOGENESIS

The pathogenesis of CVSM is not fully understood but appears to be multifactorial. Etiologic factors such as genetic predisposition, hormonal changes, nutrition, trauma, and exercise are the most investigated. Early on a genetic predisposition to CVSM in horses was suspected based on the frequency of CVSM in certain families of Thoroughbreds;[3,59] however, lack of many close relationships in a group of 47 horses with CVSM gave rise to thoughts on other etiologic factors.[1] Although some investigators have failed to demonstrate genetic determination of CVSM,[60,61] others believe that genetic factors that determine the length of the neck, cervical vertebral biomechanics, and body size play a significant role in the development of CVSM.[9,62,63] In the most recent investigation of the heritability of CVSM, Reed reported a suspicion that a genetic predisposition, wherein horses inherit increased sensitivity to environmental factors affecting cartilage growth, is likely.[64]

On postmortem examination of 30 horses with CVSM, Dimock and Errington demonstrated narrowing of the vertebral canal and noticed that commonly these horses had bony changes characteristic of degenerative joint disease, including osteoarthritis and malformation of the articular processes.[1] In this study, the importance of nutrition in the development of CVSM was suggested. Mayhew *et al.* found that horses with CVSM, to a far greater extent than control horses, had decreased differentiation of cartilage and osteopetrosis, sometimes associated

with osteonecrosis and osteoclasia.[10] These degenerative changes in the cervical vertebral articular processes and costochondral junctions of horses with CVSM were associated with osteochondrosis dissecans. He proposed CVSM to be a *performance* or *production* disease with a multifactorial etiology, comprised of genetic predisposition, overnutrition, and environmental and iatrogenic modifying factors. Similar to these findings were histopathology results of vertebrae involved in myelocompressive lesions, indicating that the lesion was an osteochondrotic type defect.[63] Osteochondrotic lesions are the result of abnormal endochondral ossification, and osteochondrosis of the articular processes may result in instability and malalignment of adjacent vertebrae, secondary osteoarthritis of the articular processes, and hypertrophy of soft tissue structures. All of these may contribute to spinal cord compression.[6,30,31,43,44]

Multiple investigators have shown that horses with CVSM have an increased incidence and severity of degenerate joint changes in the axial skeleton,[1,10,31,43] and Wagner *et al.* demonstrated that although offspring from horses with CVSM did not develop myelocompressive lesions themselves, this group did have a high incidence (45%) of osteochondrotic lesions in both the axial and appendicular skeleton.[61]

There has not been general agreement on the importance of degenerative joint disease of the cervical vertebrae in the pathogenesis of CVSM. Rooney has proposed that malformation of the articular processes is the predisposing lesion and, thus, is essential in the pathogenesis of CVSM.[9] Binkhorst, however, found only 8% correlation between lesions of the articular processes and histologic changes in the spinal cord,[43] and similar to Binkhorst's findings, Stewart *et al.* reported that the site of the most severe osteochondrotic lesions did not always correlate with the site of vertebral stenosis.[31] This suggests that osteochondrosis of the articular processes is not the direct cause of CVSM, but that the primary predisposing factor in the pathogenesis of CVSM is the insufficient diameter of the cervical vertebral canal at the site where spinal cord compression occurs. This is why Hurtig and Pool suggest CVSM is a manifestation of developmental orthopedic disease but does not belong to the osteochondrosis syndrome.[65] The positive correlation between osteochondrosis and CVSM, however, may indicate that the pathogenesis of both conditions is similar and may respond to the same preventive and therapeutic measures.[31,64]

In contrast to younger horses in which the role of degenerative joint disease in the pathogenesis of CVSM appears controversial, in older horses (>4 years) CVSM is generally associated with significant arthropathies of the caudal cervical articular processes. In these horses, the compression of the spinal cord can be attributed to the bony and soft tissue proliferation at the affected articular processes. This finding is supported by the improvement most of these horses show following medical and surgical treatment with subsequent radiographic evidence of reduction of the bony proliferation. The genesis of the degenerative joint disease in older horses with CVSM is speculative; however, currently the role of external trauma is thought to be the most important.[20]

The effects of trauma and exercise in predisposed animals are hypothesized to contribute to the development of osteochondrosis and CVSM,[48] but this view is controversial as is the role of numerous dietary factors in the development of these diseases.[66] The accelerated rate of gain, but not of growth, has been related to osteochondrosis and CVSM in horses; however, controlled investigations have failed to confirm this relationship.[67] Nutritional factors that have been associated with the incidence of developmental orthopedic disease are a dietary imbalance in the calcium/phosphorus concentration, copper deficiency, excess zinc, excess protein, and excess carbohydrate. The three most important nutritional factors appear to be excessive dietary digestible energy, excessive dietary phosphorus, and dietary copper deficiency.[66]

Excess carbohydrate in the diet is thought to contribute to developmental orthopedic disease through an endocrine imbalance involving elevation of serum insulin concentrations and decreased serum thyroxin concentrations, resulting in a lack of cartilage maturation.[68,69] Based on this hypothesis, a paced-growth program for the prevention and therapy of CVSM has been recommended in order to slow down body growth in height and weight.[48] Savage *et al.* demonstrated that high-digestible energy diets, composed of both carbohydrates and corn oil components, caused osteochondrotic lesions in foals but that these are not solely due to an excessive average daily weight gain.[70] It is suggested that feeding high-digestible energy diets

result in endocrinologic alterations that mediate local cartilaginous factors and selectively activate genes that cause a specific alteration in matrix phenotype.[66]

A dietary calcium/phosphorus imbalance has been implicated in CVSM,[43] and particularly, excessive phosphorus (388% of the requirements) appears to be correlated with an increased incidence and severity of osteochondrotic lesions in foals.[71]

Copper deficiency leads to defective lysyl oxidase, which is a copper-dependent enzyme required for proper maturation of connective tissues. A low-copper diet (15 ppm) produced 3 times as many osteochondrotic lesions of the appendicular and 7 times as many osteochondrotic lesions of the axial skeleton, as compared to foals fed a high-copper diet[67] (55 ppm); however, copper supplementation did not eliminate developmental orthopedic disease, supporting the presence of other etiologic factors. Similar results were obtained when foals fed with 7 ppm of copper had a much higher incidence of macroscopic osteochondrosis than foals fed with 30 ppm of copper.[72] Zinc has an antagonistic effect to copper and it has been postulated that diets with excessive zinc could cause secondary copper deficiency,[73] but this has not been proven in the case of horse.

CONCLUSION

Cervical vertebral stenotic myelopathy is the most common non-infectious cause of spinal cord ataxia in the horse. Stenosis of the cervical vertebral canal and subsequent myelocompression is the cause of this neurologic disease. Although the etiology of CVSM is not fully understood, diagnostics and therapeutic options for affected horses have improved over the last few years. The specificity and sensitivity of predicting CVSM from survey radiographs using the sagittal ratio method is high; however, myelography remains necessary for localization of compressive lesions. Further research is required in the field of antemortem diagnostics, that is, defining criteria to evaluate myelograms and evaluating the use of computed tomography. Ventral interbody fusion has been proven an effective surgical procedure; however, complete recovery does not occur in all horses, and risks associated with postoperative performance must be carefully considered by the owners.

REFERENCES

1. Dimock WW, Errington BJ. 1939. Incoordination of equidae: wobblers. *J Amer Vet Med Assoc* 95: 261–7.
2. Mayhew E. 1860. *The illustrated horse doctor*, London: W.H. Allen and Co.
3. Errington BJ. 1938. Causes of "Wobblers". *The Vet Bull Supp to Army Medical Bulletin* 32:153–5.
4. De Lahunta A. 1983. Veterinary neuroanatomy and clinical neurology. Philadelphia, PA: W.B. Saunders Co.
5. Nixon AJ, Stashak TS, Ingram J. 1982. Diagnosis of cervical vertebral malformation in the horse. *Proc Amer Assoc Equine Pract* 28:253–66.
6. Powers BE, Stashak TS, Nixon AJ, Yovich, *et al*. 1986. Pathology of the vertebral column of horses with cervical static stenosis. *Vet Pathol* 23:392–9.
7. Papageorges M, Gavin PR, Sande RD, *et al*. 1987. Radiographic and myelographic examination of the cervical vertebral column in 306 ataxic horses. *Vet Rad* 28:53–9.
8. Rush Moore B, Holbrook TC, Stefanacci JD, *et al*. 1992. Contrast-enhanced computed tomography and myelography in six horses with cervical stenotic myelopathy. *Equine Vet J* 24:197–202.
9. Rooney JR. 1969. "Disorders of the nervous system". In *Biomechanics in lameness*, edited by Rooney, JR, 219–33. Baltimore: Williams and Wilkins.
10. Mayhew IG, De Lahunta A, Whitlock RH, *et al*. 1978. Spinal cord disease in the horse. *The Cornell Veterinarian* 68(Suppl 6):106–142.
11. Wilson WD, Hughes SJ, Ghoshal NG, *et al*. 1985. Occipitoatlantoaxial malformation in two non-Arabian horses. *J Amer Vet Med Assoc* 187:36.
12. Reed SM, Rush BR. 1999. "Developmental vertebral anomalies". In *Equine Surgery*, edited by Auer JA, Stick JA, 423–8. Philadephia, PA: W.B. Saunders.
13. Mayhew IG. 1996. Equine neurology and nutrition. *Proc. A.E.V.A. Bain-Fallon Memorial Lectures* 18:1–73.
14. Chiapetta JR, Baker JR, Feeney DA. 1985. Vertebral fracture, extensor hypertonia of thoracic limbs, and paralysis of the pelvic limbs (Schiff-Sherrington syndrome) in an Arabian foal. *J Amer Vet Med Assoc* 186:387.
15. Rashmir-Raven A, DeBowes RM, Hudson L, *et al*. 1991. Vertebral fracture and paraplegia in a foal. *Prog Vet Neurol* 2:197–202.
16. Pinchbeck G, Murphy D. 2001. Cervical vertebral fracture in three foals. *Equine Vet Educ* 1:24–8.

17. Schott II HC, Major MD, Grant BD, *et al*. 1990. Melanoma as a cause of spinal cord compression in two horses. *J Amer Vet Med Assoc* 196:1820–2.
18. Furr MO, Anver M, Wise M. 1991. Intervertebral disk prolapse and diskospondylitis in a horse. *J Amer Vet Med Assoc* 198:2095–6.
19. Colbourne CM, Raidal SL, Yovich JV, *et al*. 1997. Cervical Discospondylitis in two horses. *Aust Vet J* 75:477–9.
20. Mayhew IGJ. 1999. The diseased spinal cord. *Proc Amer Assoc Equine Pract* 45:66–84.
21. Yovich JV, Powers BE, Stashak TS. 1985. Morphologic features of the cervical intervertebral disks and adjacent vertebral bodies of horses. *Amer J Vet Res* 46:2372–7.
22. Allison N, Moeller Jr. RB. 2000. Spinal ataxia in a horse caused by an arachnoid diverticulum (cyst). *J Vet Diag Invest* 12:279–81.
23. Reed SM, Robertson J, Grant B. Unpublished observations.
24. Wagner PC, Grant BD, Reed SM. 1987. Cervical vertebral malformation. *Vet Clin North Amer Equine Pract* 3:385–96.
25. Rush Moore B, Reed SM, Robertson JT. 1993. Surgical treatment of cervical stenotic myelopathy in horses: 73 cases (1983–1992). *J Amer Vet Med Assoc* 203:108–12.
26. Mayhew IG, Donawick WJ, Green SL, *et al*. 1993. Diagnosis and prediction of cervical vertebral malformation in thoroughbred foals based on semiquantitative radiographic indicators. *Equine Vet J* 25:435–40.
27. Rush Moore B, Reed SM, Biller DS, *et al*. 1994. Assessment of vertebral canal diameter and bony malformations of the cervical part of the spine in horses with cervical stenotic myelopathy. *Amer J Vet Res* 55:5–13.
28. Van Biervliet, Mayhew J, de LaHunta A. 2006. Cervical vertebral compressive myelopathy. *Clin Tech Equine Prac* 5:54–9.
29. Reed SM, Newberry J, Norton K, *et al*. 1985. Pathogenesis of cervical vertebral malformation. *Proc Amer Assoc Equine Pract* 31:37–42.
30. Gerber H, Ueltschi G, Diehl M, *et al*. 1989. Untersuchungen an der Halswirbelsäule des Pferdes - eine klinisch-radiologische Studie. *Schweiz Arch Tierheilk* 131:311–21.
31. Stewart RH, Reed SM, Weisbrode SE. 1991. Frequency and severity of osteochondrosis in horses with cervical stenotic myelopathy. *Amer J Vet Res* 52:873–9.
32. Newton-Clarke MJ, Divers TJ, De Lahunta A, *et al*. 1994. Evaluation of the thoraco-laryngeal reflex ('slap test') as an aid to the diagnosis of cervical spinal cord and brainstem disease in horses. *Equine Vet J* 26:358–61.
33. Tomizawa N, Nishimura R, Sasaki N, *et al*. 1994. Efficacy of the new radiographic measurement method for cervical vertebral instability in wobbling foals. *J Vet Med Sci* 56:1119–22.
34. Andrews FM, Adair III HS. 1999. "Anatomy and physiology of the nervous system." In *Equine Surgery*, edited by Auer JA, Stick JA, 405–12, Philadelphia, PA: W.B. Saunders.
35. Andrews FM, Matthews HK, Reed SM. 1990. The ancillary techniques and tests for diagnosing equine neurologic disease. *Vet Med* Dec:1325–30.
36. Furr MO, Tyler RD. 1990. Cerebrospinal fluid creatine kinase activity in horses with central nervous system disease: 69 cases (1984–1989). *J Amer Vet Med Assoc* 197:245–8.
37. Furr M, Chickering WR, Robertson J. 1997. High resolution protein electrophoresis of equine cerebrospinal fluid. *Amer J Vet Res* 58:939–41.
38. Pavlov H, Torg IS, Robie B, *et al*. 1987. Cervical spinal stenosis: Determination with vertebral body ratio method. *Radiology* 164:771–5.
39. Mayhew IG, Green SL. 2002. Radiographic diagnosis of equine cervical vertebral malformation. *Proc 20th Annual Meet Amer Coll Vet Intern Med,* 382–3.
40. Neuwirth L. 1992. Equine myelography. *Compend Contin Educ Pract Vet* 14:72–8.
41. Nyland TG, Blythe LL, Pool RR, *et al*. 1980. Metrizamide myelography in the horse: clinical, radiographic, and pathologic changes. *Amer J Vet Res* 41:204–11.
42. Van Biervliet J, Scrivani PV, Divers TJ, *et al*. 2002. Evaluation of a diagnostic criterion for spinal cord compression during cervical myelography. *Proc 20th Annual Meet Coll Vet Intern Med,* 769.
43. Binkhorst GJ. 1976. Het ataxiesyndroom bij jonge paarden *Inaugural Dissertation*, Utrecht University.
44. Gruys E, Beynen AC, Binkhorst GJ, *et al*. 1994. Neurodegeneratieve aandoeningen van het centrale zenuwstelsel bij het paard. *Tijdschr Diergeneesknd* 119:561–7.
45. Yovich JV, Gould DH, LeCouteur RA. 1991. Chronic cervical compressive myelopathy in horses: patterns of astrocytosis in the spinal cord. *Aust Vet J* 68:334–7.
46. Tomizawa N, Nishimura R, Sasaki N, *et al*. 1994. Relationships between radiography of cervical vertebrae and histopathology of the cervical cord in wobbling 19 foals. *J Vet Med Sci* 56:227–33.
47. Yovich JV, LeCouteur RA, Gould DH. 1991. Chronic cervical compressive myelopathy in

horses: clinical correlations with spinal cord alterations. *Aust Vet J* 68:326–34.
48. Donawick WJ, Mayhew IG, Galligan DT, *et al*. 1989. Early diagnosis of cervical vertebral malformation in young Thoroughbred horses and successful treatment with restricted, paced diet and confinement. *Proc Amer Assoc Equine Pract* 35:525–8.
49. Kronfeld DS, Meacham TN, Donoghue S. 1990. Dietary aspects of developmental orthopedic disease in young horses. *Vet Clin North Am Equine Pract* 6:451–65.
50. Mayhew IG, Brown CM, Stowe HD, *et al*. 1987. Equine Degenerative Myeloencephalopathy: a vitamin E deficiency that may be familial. *J Vet Int Med* 1:45–50.
51. Grisel GB, Grant BD, Rantanen NW. 1996. Arthrocentesis of the equine cervical facets. *Proc Amer Assoc Equine Pract* 42:197–8.
52. Grant BD. 1999. "Surgical treatment of developmental disorders of the spinal column". In *Equine Surgery*, edited by Auer JA, Stick JA, 429–35, Philadelphia, PA: W.B. Saunders.
53. Wagner PC, Bagby GW, Grant BD, *et al*. 1979. Surgical stabilization of the equine cervical spine. *Vet Surg* 8:7–12.
54. DeBowes RM, Grant BD, Bagby GW, *et al*. 1984. Cervical vertebral interbody fusion in the horse: a comparative study of bovine xenografts and autografts supported by stainless steel baskets. *Amer J Vet Res* 45:191–9.
55. Kumar VG, Rea GL, Mervis LJ, *et al*. 1999. Cervical spondylotic myelopathy: functional and radiographic long-term outcome after laminectomy and posterior fusion. *Neurosurgery* 44:771–7; discussion 777–8.
56. Hacker RJ. 2002. Threaded cages for degenerative cervical disease. *Clin Ortho Rel Res* 394:39–46.
57. Rusbridge C, Wheeler SJ, Torrington AM, *et al*. 1998. Comparison of two surgical techniques for the management of cervical spondylomyelopathy in Dobermans. *J Small Anim Pract* 39:425–31.
58. Nixon AJ, Stashak TS. 1988. Laminectomy for relief of atlantoaxial subluxation in four horses. *J Amer Vet Med Assoc* 193:677–82.
59. Dimock WW. 1950. "Wobblers"—an hereditary disease in horses. *J Hered* 41:319–23.
60. Falco MJ, Whitwell K, Palmer AC. 1976. An investigation into the genetics of "Wobbler disease" in thoroughbred horses in Britain. *Equine Vet J* 8:165–9.
61. Wagner PC, Grant BD, Watrous BJ, *et al*. 1985. A study of the heritability of cervical vertebral malformation in horses. *Proc Amer Assoc Equine Pract* 31:43–50.
62. Rooney JR. 1972. Etiology of the wobbler syndrome. *Mod Vet Pract* 53:42.
63. Nixon AJ. 1999. Cervical vertebral malformation and malarticulation. In *Equine Medicine and Surgery,* edited by Colahan PT, Merritt AM, Moore JN, Mayhew IG, 957–971, St Louis, Mosby.
64. Reed SM. 1997. Cervical vertebral stenotic myelopathy: pathogenesis. *Proc Inter Equine Neurol Conf* July:45–9.
65. Hurtig MB, Pool RR. 1996. "Pathogenesis of equine osteochondrosis". In *Joint disease in the horse*, edited by McIllwraith CW, Trotter GW, 335–8, Philadephia, PA: W.B. Saunders Co.
66. Savage CJ. 1998. "Etiopathogenesis of osteochondrosis". In *Current techniques in equine surgery and lameness*, edited by White II NA, Moore JN, 318–22, Philadephia, PA: W.B. Saunders Co.
67. Knight D, Weisbrode SE, Schmall LM, *et al*. 1990. The effects of copper supplementation on the prevalence of cartilage lesions in foals. *Equine Vet J* 22:426–32.
68. Glade MJ, Belling Jr. TH. 1984. Growth plate cartilage metabolism, morphology and biochemical composition in over- and underfed horses. *Growth* 48:473–82.
69. Glade MJ, Luba NK. 1987. Serum triiodothyronine and thyroxine concentrations in weanling horses fed carbohydrate by direct gastric infusion. *Amer J Vet Res* 48:578–82.
70. Savage CJ, McCarthy R, Jeffcott L. 1993. Effects of dietary energy and protein on induction of dyschondroplasia in foals. *Equine Vet J(Suppl* 16):74–9.
71. Savage CJ, McCarthy R, Jeffcott L. 1993. Effects of dietary phosphorus and calcium on induction of dyschondroplasia in foals. *Equine Vet J(Suppl* 16):80–3.
72. Hurtig MB, Green SL, Dobson H. 1993. Correlative study of defective cartilage and bone growth in foals fed a low-copper diet. *Equine Vet J(Suppl* 16):66–73.
73. Knight DA, Gabel AA, Reed SM, *et al*. 1985. Correlation of dietary mineral to incidence and severity of metabolic bone disease in Ohio and Kentucky. *Proc Amer Assoc Equine Pract* 31:445–61.

23
Congenital Malformation of the Nervous System

Martin Furr

Malformations of the central nervous system (CNS) are reported to be common,[1] yet few reports exist in the equine literature, and congenital CNS malformations appear to be rare in the horse. In one survey of 773 equine fetuses or foals less than five days of age, the occurrence of congenital defects was 38/773 (4.9%).[2] A single case of nervous system abnormality was found—a foal with cerebral agenesis. A single case of spinal dysraphism was reported in another survey.[3] In another study comprised of 608 foals with congenital defects which resulted in death, hydrocephalus was found in 3%, and cleft cranium with meningoencephalocele was observed in 1.6%.[4] Deformed fetuses represented only 6.79% of the total number of foals examined during the study period. Exposure to infectious agents, teratogenic chemicals, and plant teratogens have been described as potential causes, although the cause in most cases remains undetermined.

BRAIN

Numerous disorders of brain development are described in veterinary species, each of which may result in variable degrees of cranial nerve disorders. Cerebellar and cerebral hypoplasia and hydrocephalus were observed in two aborted equine fetuses secondary to hydrops allantois.[5] Cerebral hypoplasia with an associated meningoencephalocele was observed in a Belgian foal that was born dead, and cerebral agenesis was described in another foal which was born dead.[1,2] Agenesis of the corpus collosum with cerebellar hypoplasia has been described in a foal which presented with seizures and altered mental status immediately after birth.[6] In addition to the seizures, an erratic breathing pattern was observed. The foal had a wide, dome-shaped forehead, which was otherwise normal in appearance. CT scanning confirmed agenesis of the corpus collosum. The foal survived but had persistent ataxia, nystagmus, occasional intention tremors, and became aggressive, prompting euthanasia. Postmortem examination confirmed the CT findings and the diagnosis of Dandy-Walker syndrome.

Congenital encephalomyelopathy was observed in a Quarter Horse foal.[7] The foal was affected at birth, was unable to stand and had coarse rhythmic rear limb tremors that were exaggerated when the foal was assisted into a standing position. Vital parameters and mentation were normal. Forelimb reflexes were normal; however, rear limb reflexes (patellar reflex) were exaggerated bilaterally. Blood and cerebrospinal fluid evaluation were unremarkable. Postmortem examination found no gross abnormalities, but histologic examination found enlarged axons in all white matter tracts, with myelin degeneration. Astrocytosis and gliosis were seen as well.[7] The cause of the disorder was not determined, but a genetic disorder was suspected, as the dam had produced two other foals with similar clinical signs.

Hydrocephalus

Hydrocephalus is defined as an increase in the volume of cerebrospinal fluid (CSF), which can be classified as either compensatory or obstructive (internal). Obstructive hydrocephalus can be observed following aqueductal stenosis or may be seen secondary to suppurative bacterial meningitis or cholesterol granulomas in older animals. In compensatory hydrocephalus, the CSF increases in volume to replace parenchyma that has been destroyed or failed to

develop.[1] Congenital hydrocephalus has been recognized in neonatal foals.[8–12]

Congenital hydrocephalus in foals appears to be rare and can be of variable severity. Hydrocephalus represented 3.0% of all congenital abnormalities of neonatal foals in one survery.[4] Many foals are aborted or born dead[9] as hydrocephalus is often associated with dystocia due to the grossly enlarged head.

Hydrocephalus may be inherited, as one Standardbred stallion produced seven hydrocephalic foals out of a foal crop of 239.[9] Inadequate numbers of foals were available for a full evaluation; however, the authors concluded that it was unlikely to be an X-linked or single autosomal recessive defect.[9]

Clinical signs resulting from hydrocephalus are variable. Foals may be born dead, or they may be normal initially and then may develop clinical signs later (hours to days). Clinical signs reflect cerebral disease and include dullness, blindness, strabismus, and nystagmus. Seizures may be seen as well.

Diagnosis is done by observation and is aided in less obvious cases by radiography. An amorphous *ground glass* appearance may be seen, along with very thin cranial bones and the presence of open areas which may be associated with fontanels. Palpation of the skull may reveal open fontanels or areas of bone defect in the cranium. Ultrasonagraphy can be used for confirmation.[8]

Treatment of internal hydrocephalus has been attempted in one reported case, using a ventricular stent tunneled to the thoracic cavity to drain excess CSF. Although drainage of the excess CSF was achieved, the thoracic drain could not be placed, and the foal was euthanized the first postoperative day due to complications and a grave prognosis.[8]

SPINE AND SPINAL CORD

Malformations of the spine appear to be relatively uncommon in horses, and they include kyphosis, scoliosis, and lordosis. In a postmortem survey of 443 horses with thoracolumbar disease, only 2.9% demonstrated these abnormalities.[13] The incidence of neurological signs associated with these bony malformations was not reported, but is considered to be small. The most commonly recognized syndrome is the occipito-atlanto-axial malformation (OAAM). Summers *et al*. report a foal with myelodysplasia and vertebral scoliosis.[1] The foal was reported to have no observable gait abnormality. Cervical spina bifida associated with meningocele has been reported in an Appaloosa foal.[14] Other forms of myelodysplasia of the equine spinal cord have been reported including syringomyelia in a thoroughbred foal.[15] A prominent bunny-hopping gait with spasticity was observed in this foal.[15] Congenital deviation of the axial skeleton has been observed in foals with arthrogryposis.

Butterfly vertebrae, hemivertebrae, and block vertebrae have all been described in foals, with variable degrees of neurologic compromise. Hemivertebrae are wedge-shaped vertebrae in which the apex may be directed ventrally, laterally, or dorsally, resulting in kyphosis, scoliosis, or lordosis.[16,17] Hemivertebrae and multiple thoracic vertebral abnormalities were found in a Quarter Horse foal which presented for a long-standing hind limb ataxia when it was five months and which had recently worsened.[17] There was severe kyphosis at the mid-thoracic level, with fusion of the dorsal spinous processes of T4–T8. Myelography confirmed compression at T7. Hemivertebrae have been described in a variety of locations; however, the mid-thoracic region appears to be the most commonly involved. Block vertebrae are fused vertebral bodies that appear to arise due to a failure of segmentation, while butterfly vertebrae demonstrate a dorsal to ventral cleft. These anomalies are apparently very rare in the horse and do not appear to cause significant clinical signs.

Occipito-atalanto-axial Malformation

Occipito-atalanto-axial malformation describes the syndrome of congenital disorders of the occiput, atlas and axis. Although there are a number of variations, the basic abnormality involves fusion of the atlas and occiput and hypoplasia of the atlas and dens.[18] Subluxation and scoliosis are variably seen.

Four basic subtypes of the anomaly are observed: (1) occipitalization (occipital bone-like modification) of the atlas and atlantization (atlas bone-like modification) of the axis (familial in Arabian horses), (2) asymmetric malformations, (3) asymmetric atlanto-axial fusion, and (4) OAAM with two atlases. A fifth type has been described which is comprised of changes similar to the familial Arabian form, but in non-Arabian horses.[19] Congenital luxation of the atlanto-axial articulation has also been described, resulting in signs of severe spinal ataxia and weakness in a neonate.[20]



Figure 23.1. Figure A above is that of a normal 3 week old foal. B. This foal demonstrates occipitoatalantoaxial malformation. The dens is malformed and appears subluxated, and the atlas is malformed. Photo courtesy of Dr. Robert MacKay.

Clinical neurological signs in affected individuals can vary in onset and severity. Some affected horses may have only scoliosis without neurologic gait deficits.[18] Foals may be born dead due to compression of the medulla oblongata and spinal cord by unstable osseous structures, and the development of clinical signs may be delayed considerably. In the familial form, horses are usually noted to be affected at birth, but signs may not appear until later in life.[18] For example, clinical signs of pelvic limb ataxia did not develop until the horse. was three years old. A 3-year-old Quarter Horse had been ridden and shown successfully prior to demonstrating signs of incoordination and weakness.[19]

Typically, neurologic abnormalities involve various degrees of ataxia and tetraparesis. Cutaneous hypalgesia of the cranial cervical area may be present, and scoliosis is variably present. In most cases, the horses have an abnormal head and neck carriage, with the neck extended. The atlas is usually

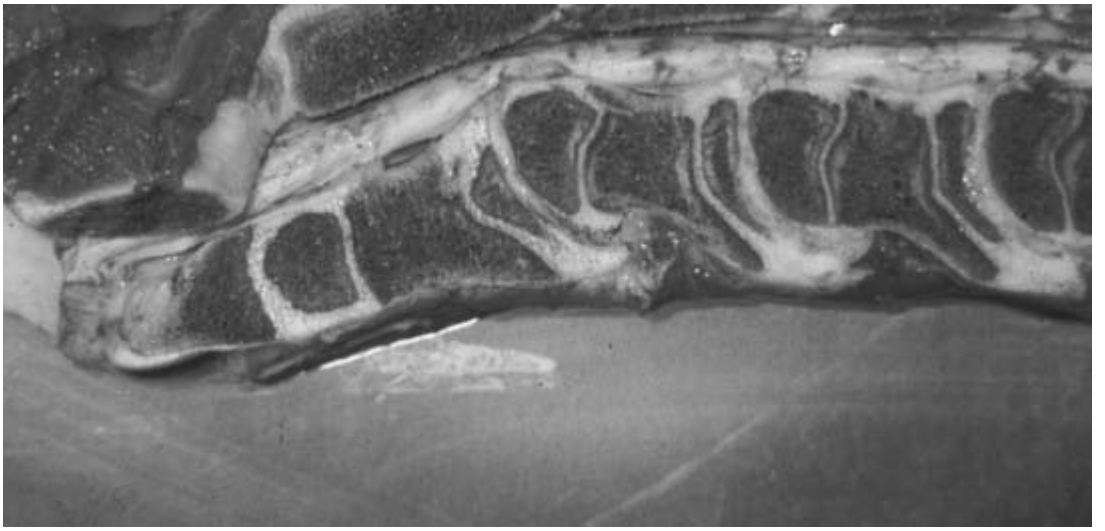


Figure 23.2. Sagittal section of the cervical spine of a foal. Note the wedge-shaped malformed cervical vertebra resulting in spinal compression.

palpably abnormal, and there may be visible swellings. An audible clicking sound is often heard when the horses' head is moved, associated with recurrent subluxation.

Diagnostic rule-outs include cervical trauma, other congenital malformations of the spinal cord, and cerebellar hypoplasia. Cervical compressive myelopathy should be considered, but this usually does not become apparent until later in life. Cerebellar hypoplasia can be differentiated by presence of intention tremors and dysmetria which are absent in horses with OAAM. The diagnosis is confirmed by taking radiography of the head and cranial cervical spine. Successful treatment has not been reported, and those cases with severe neurologic signs should be destroyed. Although not confirmed, it is considered that the defect in Arabian horses is hereditary; hence, affected horses should not be used for breeding.

REFERENCES

1. Summers BA. 1995. Malformations of the central nervous system. In *Veterinary Neuropathology*, edited by Summers BA, Cummings JF, de Lahunta A,68–94. St Louis, MO: Mosby.
2. Collobert-Laugier C, Tariel G. 1993. Congenital abnormalities in foals. *Pratique Vet Equine* 25: 105–10.
3. Huston R, Saperstein G, Leipold HW. 1977. Congenital defects in foals. *J Eq Med Surg* 1:146–61.
4. Crowe MW, Swerczek TW. 1985. Equine congenital defects. *Am J Vet Res* 46:353–8.
5. Waelchli RO, Ehrensperger F. 1988. Two related cases of cerebellar abnormality in equine fetuses associated with hydrops of fetal membranes. *Vet Rec* 123:513–4.
6. Cudd TA, Mayhew IG, Cottrill CM. 1989. Agenesis of the corpus collosum with cerebellar vermian hypoplasia in a foal resembling the Dandy-Walker syndrome: pre-mortem diagnosis by clinical evaluation and CT scanning. *Equine Vet J* 21: 378–81.
7. Seahorn TL, Fuentealba IC, Illanes OG*, et al.* 1991. Congenital encephalomyelopathy in a Quarter Horse. *Equine Vet J* 23:394–6.
8. Foreman JH, Reed SM, Rantanen NW. 1983. Congenital internal hydrocephalus in a Quarter horse foal. *J Equine Vet Sci* 3:154–64.
9. Ojala M, Ala-Huikku J. 1992. Inheritance of hydrocephalus in horses. *Equine Vet J* 24:140–3.
10. Bester RC, Cimprich RE, Evans LH. 1976. Hydrocephalus in an 18-month-old colt. *J Amer Vet Med Assoc* 168:1041–2.
11. Bowman RW. 1980. Congenital hydrocephalus in 2 foals. *Mod Vet Pract* 61:862–4.
12. Carbery JT. 1979. A case of equine hydrocephalus. *New Zealand Vet J* 27:158.

13. Jeffcoat LB. 1980. Disorders of the thoracolumbar spine of the horse—a survey of 443 cases. *Equine Vet J* 12:197–210.
14. Leathers CW, Wagner PC, Milleson BD. 1979. Cervical spina bifida with meningocele in an Appaloosa foal. *J Vet Orthop* 1:55–8.
15. Cho DY, Leipold HW. 1977. Syringomyelia in a thoroughbred foal. *Equine Vet J* 9:195–7.
16. Boyd JS. 1976. Congenital Deformities in two Clydesdale foals. *Equine Vet J* 8:161–4.
17. Wong DM, Scarratt WK, Rohleder J. 2005. Hindlimb paresis associated with kyphosis, hemivertebrae and multiple thoracic vertebral malformations in a Quarter Horse gelding. *Equine Vet Ed* 17:187–94.
18. Mayhew IG, Watson AG, Heissan JA. 1978. Congenital occipitoatlantoaxial malformations in the horse. *Equine Vet J* 10:103–13.
19. Wilson WD, Hughes SJ, Ghoshal NG*, et al.* 1985. Occipitoatlantoaxial malformation in two non-Arabian horses. *J Am Vet Med Assoc* 187:36–40.
20. Witte S, Alexander KA, Bucellato M*, et al.* 2005. Congenital atlantoaxial luxation associated with malformation of the dens axis in a Quarter Horse foal. *Equine Vet Ed* 17:175–8.

24
Central Nervous System Trauma

Yvette Nout

Trauma to the central nervous system (CNS) is the most common cause of neurologic disease in horses. A recent study reported that CNS trauma accounted for 22% of equine neurologic disorders,[1] which is consistent with the findings of previous studies that reported CNS trauma accounted for 24% of neurological cases.[2] Both studies reported trauma to the spinal cord to be more prevalent than brain injury. Feige *et al*.[1] reported a diagnosis of traumatic brain injury (TBI) in 5 of 22 (23%) horses that were presented for traumatic neurologic disease, whereas 17 of 22 (77%) were diagnosed with spinal cord injury (SCI). Tyler *et al*.[2] reported 47 cases of TBI and cranial nerve disease in 107 (44%) horses examined, whereas 60 horses in this group had SCI (56%). Although mechanisms of CNS cell damage, to a certain degree, are similar after TBI and SCI, there are a few processes with regard to etiology and pathophysiology that are more specific for either TBI or SCI. Clinical syndromes as a result of traumatic injury to the CNS can vary tremendously, but the most common are coma, vestibular disease, tetra- and paraparesis or -plegia, and cauda equina. Treatment regimens of CNS injury are aimed toward reducing inflammation and swelling, halting secondary injury mechanisms, and promoting regeneration and recovery of function. Prognosis depends primarily on severity of primary injury and on the extent and neuroanatomic location of CNS damage.

ETIOLOGY

Traumatic Brain Injury

Head trauma is typically caused by incidents such as collision with an immovable object (e.g., fence posts or another horse), falling down, flipping over backward, being kicked by another horse, and, although rare, impact by a projectile (e.g., gunshot). Another type of head injury that may lead to CNS damage is fracture of the petrous temporal bone associated with temporohyoid osteoarthropathy.[3,4] This syndrome is fully discussed in Section 2, Chapter 8. Classification of TBI is summarized in Table 24.1.

Although traumatic injury to the head is reported to be common in horses, subsequent CNS injury does not occur in all cases—in one report, half of the cases presented for head trauma had evidence of TBI.[5] The remaining horses typically present for fractures of the orbit, periorbital rim, and zygomatic, mandibular, or maxillary bones.[5,6] Impact to the head causes bony deformation, which may be transient or may result in subsequent fracture or separation of the bones of the calvarium. Fractures may be linear, stellate, compound, comminuted, or depressed. TBI may occur with or without fracture of the calvarium, however, and some of the most severe injuries to the brain occur when the injury is contained within the closed calvarium (i.e., no skull fractures).[7] Within the closed calvarium, the sum of the intracranial volumes of the brain, blood, and cerebrospinal fluid (CSF) is constant and volume or pressure changes within one of these compartments will affect volume (anatomy) or pressure of the other compartments. For example, the presence of hematomas or brain swelling after trauma will rapidly lead to increased intracranial pressure with subsequent reduction of cerebral perfusion pressure and cerebral blood flow and/or further damage or herniation of brain matter.

Consequences of impact sustained to the poll in horses that flip over backward include fracture of

Table 24.1. Classification of Traumatic Brain Injury (TBI)

Mechanism	Blunt	High/low velocity
	Penetrating	
	Blast	
Severity	Mild	
	Moderate	Neurologic examination
	Severe	
Morphology	Skull fracture	Vault
		Basilar
	Intracranial	Local
		Diffuse (concussion, diffuse axonal injury)

the bones on the side and base of the calvarium such as the petrous temporal, squamous temporal, and parietal bones. More commonly, these bones remain intact, and more serious injury occurs to the basilar bones as a result of strong traction forces from the rectus capitis ventralis muscles.[4,8,9] These paired muscles are the main flexors of the head; they originate at the cervical vertebrae and insert in the ventral aspect of the basioccipital and basisphenoid bones. Sudden extension of the head stretches these muscles, which commonly results in fracture of the bony tubercles from the basilar bones. Additionally, adjacent large vessels are lacerated, and hemorrhage into the retropharyngeal spaces or guttural pouches can occur. In severe cases, transverse fracture of the basilar bones at the level of the basioccipital–basisphenoidal suture can occur. Young horses may be more susceptible to this type of injury because the joint between the basilar bones fuses by 5 years of age.[9] In most cases, the fracture site is stable and minimal displacement occurs. Despite this, serious damage of associated soft tissue such as subdural or subarachnoid bleeding around the brainstem and cranial nerve damage may occur. The cerebellum is seldom severely damaged after poll impact,[4] but the cerebral parenchyma is more commonly injured after being subjected to rapid acceleration–deceleration forces. Moreover, optic nerves and other attachments may be torn from the cerebral hemispheres.[10]

Impact to the dorsal surface of the head may result in damage to the frontal or parietal bones with subsequent cerebral cortical injury or, more commonly, damage to the cervical vertebrae with subsequent SCI.[4] Also, cranial nerve XII may be injured as it exits the hypoglossal foramen. Furthermore, occipital cortical injury may occur, and as described for poll impact injuries, with frontal injuries, the optic nerves may be stretched.

Temporohyoid osteoarthropathy is a chronic condition in which fusion of the temporal and stylohyoid bones, stricture of the external ear canal, and obliteration of the lumen of the tympanic bullae occurs.[11–14] Forces applied to this immobilized joint can cause fractures of the skull of which a common sequela is damage to the vestibular apparatus or cranial nerve VII. Another sequela is extension of infection in the middle/inner ear to the brainstem, additional cranial nerves, or hindbrain. Temporohyoid osteoarthropathy is fully discussed in Section 2, Chapter 6.

Spinal Cord Injury

Trauma to the vertebral column is typically caused by incidents such as collision with an immovable object or falling down. Injury to the vertebral column can occur at all sites, but trauma to or fractures of the cervical vertebrae are the most common.[1,2,7,15] Foals appear to be more susceptible to vertebral trauma than adults and frequently suffer injury to the cranial cervical (C1–3) and caudal thoracic (T15–18) regions.[7] Fractures elsewhere along the vertebral column occur as well, and a recent report describes vertebral fractures between C3 and C6 in three foals.[16] Vertebral fracture with subsequent SCI, not as a result of trauma but secondary to osteomyelitis, occurs and has recently been reported in a foal at the level of T10.[17] Predilection sites for vertebral trauma in adult horses are the occipital–atlanto–axial region, the caudal cervical region (C5–T1), and the caudal thoracic region.[7,15] Again, reports of injury at other sites along the vertebral column exist, such as fractures to the sacral[18,19] and coccygeal[20,21] regions.

Hyperextension, hyperflexion, dislocation, and compression of the vertebral column can result in varying severities of osseous damage and/or SCI. When a horse nosedives with the head under the body, neck hyperflexion can lead to damage in the occipital–atlanto–axial and caudal cervical regions. SCI however may or may not be associated with fracture of the vertebrae, and injury at the level of the occipital–atlanto–axial site is frequently not associated with fracture.[15] Tearing or avulsion of the ligaments of the dens can result in severe compression of the spinal cord at the level of the occipital–atlanto–axial region. Injury to the caudal cervical spinal cord is associated not always with fracture but with local hemorrhage subsequent to the primary insult. Fractures of the mid-thoracic to cranial lumbar region are often associated with tremendous forces sustained when a horse lands on its back. These fractures are often unstable; however, in horses, muscle spasms can temporarily stabilize these lesions.[15]

Typically, the more severe the insult, the more damaged the vertebral column. The more severe clinical signs are due to soft tissue damage and osseous fragments compressing the spinal cord. With very severe injury, soft tissue structures supporting the vertebral column may be disrupted, resulting in dislocation of vertebrae. Both subluxation and luxation of vertebrae have been reported in horses.[22] There is an increased incidence of luxations, subluxations, and epiphyseal separations in young horses that is likely due to the fact that cervical vertebral growth plate closure does not occur until 4–5 years of age.[7] Compression injuries are associated with shortening of the vertebral body and result from a head-on collision with an immovable object.

PATHOPHYSIOLOGY

There is no primary literature describing or investigating the pathophysiology of traumatic injury to the CNS of the horse. Based on the evidence that similar processes are involved in all mammals, the following discussions of the pathophysiology of traumatic injury to the CNS of the horse are extrapolated from research in other animals and humans.

Traumatic Brain Injury

After trauma, forces are transmitted to the intracranial soft tissues, and the brain is consequently shaken within the uneven bony interior of the skull and/or directly damaged by osseous fragments or foreign bodies. Most severe damage generally takes place at the place of impact (coup) and/or opposite to the side of impact (contrecoup). Additionally, the brain is subjected to other forces after trauma, such as rotational and shock wave forces. TBI is a result of both direct, immediate mechanical disruption of brain tissue (primary injury) and indirect, delayed (secondary) injury mechanisms.

The primary damage is a result of the biomechanical effects of the injury and is characterized by immediate and often irreversible damage to neuronal cell bodies, dendritic arborizations, axons, glial cells, and brain vasculature. This initial brain injury may be focal, multifocal, or diffuse. Focal brain injury is typically associated with blows to the head leading to cerebral contusions, lacerations, and epidural, subdural, and intracerebral hematomas. In contrast, diffuse brain injury includes traumatic axonal injury that can occur following moderate to severe TBI and that results from forces that rapidly rotate and deform the brain.[23,24] Diffuse axonal injury is a significant component of TBI, and injured axons can display delayed axonal swelling, impairments in axonal transport, and eventual disconnection. Diffuse axonal injury is widely considered the most important pathology in severely brain-injured humans and accounts for a high percentage of mortality due to brain trauma. Most lesions associated with diffuse axonal damage, however, are microscopic; in people, the clinical diagnosis is based on prolonged unconsciousness unaccompanied by an intracranial mass lesion.[25] A direct consequence of the initial shock is thought to be the depolarization of cells through membrane mechanoreceptors. Neuronal depolarization spreads throughout the cortex and causes the transient coma characteristic of severe concussion.

Secondary injury is a complex cascade of molecular, cellular, and biochemical events that can occur for days to months following the initial insult, resulting in delayed tissue damage. In addition, systemic alterations further contribute to the tissue damage. Hypoxia, ischemia, brain swelling, alterations in intracranial pressure, hydrocephalus, infection, breakdown of blood–brain barrier (BBB), impaired energy metabolism, altered ionic homeostasis, changes in gene expression, inflammation, and activation/release of autodestructive molecules occur and exacerbate the initial injury.

Vascular damage that occurs after head injury can occur epidural (between the dura mater and the skull), subdural (between the dura mater and arachnoid mater), subarachnoid (between arachnoid mater and pia mater), superficial (vessels immediately under the pia mater), intraparenchymal, or intraventricular. Subarachnoid hemorrhage, or hemorrhage into the CSF, occurs commonly in horses.[6] Hematoma formation is of special concern because of the potential for devastating expansion within the rigid calvarium, as can occur with edema. These processes displace brain tissue, with possible sequelae being herniation, pressure necrosis, and brainstem compression. Additionally, hemorrhage around the interventricular foramen or mesencephalic aqueduct may obstruct CSF outflow and lead to hydrocephalus. Furthermore, the elevation of intracranial pressure after TBI due to hemorrhage and development of edema is of particular concern.

Principles of increased intracranial pressure are described in the Monro–Kellie doctrine, which states that once the fontanelles and sutures of the skull are closed, the brain is enclosed in a nonexpandable case of bone. The brain parenchyma is nearly incompressible, and the blood volume in the cranial cavity is therefore nearly constant. Hence, a continuous outflow of venous blood from the cranial cavity is required to make room for continuous incoming arterial blood.[26] Blood flow to the brain is controlled by changes in the diameter of resistance blood vessels, and cerebral blood flow is controlled by autoregulation whereby the perfusion pressure is maintained within a range of approximately 50–150 mmHg.[27] Beyond these limits, cerebral blood flow decreases at pressures below the lower limit and increases at pressures above the higher limit. Cerebral perfusion pressure (mean arterial blood pressure minus intracranial pressure) is the stimulus to which the autoregulatory response of the vasculature occurs. Cerebral autoregulation is altered unpredictably after TBI, and it appears that the minimum acceptable cerebral perfusion pressure is higher than normal after trauma. Increased intracranial pressure leads to a decreased cerebral perfusion pressure and subsequently reduces cerebral blood flow. Reduced cerebral blood flow results in areas of ischemia and subsequent restriction of delivery of substrates such as oxygen and glucose to the brain. Reduced cerebral blood flow has been associated with an unfavorable neurological outcome in humans and has been implicated in increased susceptibility of the brain to secondary injury.[28,29]

The cascade of secondary injury that results in necrotic and apoptotic cell death is described in more detail in Section "SCI" of "Pathophysiology." Uncontrolled glutamate release and failure of energy systems in neuronal and supporting tissues lead to elevated intracellular calcium concentrations and subsequent cell death. Hemorrhage, ischemia, and the primary tissue damage lead to the sequestration of vasoactive and inflammatory mediators at the injury site and are thus involved in the secondary injury cascade. Inflammation and endothelial damage causes derangements in normal cerebrovascular reactivity and contribute to a mismatch of oxygen delivery to tissue demand, resulting in local or diffuse ischemia.

A major consequence of ischemia is reduced delivery of oxygen and glucose. Blood flow interruption is responsible for disruption in ion homeostasis (especially calcium, sodium, and potassium) and a switch to anaerobic glycolysis resulting in lactic acid production and acidosis. Cell membrane lipid peroxidation with subsequent prostaglandin and thromboxane synthesis, formation of reactive oxygen species, nitric oxide (NO), and energy failure also ensue. Because of the high metabolic rate and oxygen demand of the brain, disruption of blood flow rapidly compromises the energy-supplying processes and leads to impaired nerve cell function and even cell death. Impaired mitochondrial function with subsequent energy depletion leads to a loss in maintenance of membrane potentials resulting in the depolarization of neurons and glia.[30] Cytotoxic edema develops through the failure of the sodium–potassium ATPase-dependent pump in the presence of hypoxia and the subsequent influx of water that passively follows sodium and chloride. This type of edema occurs in gray and white matter and decreases the extracellular fluid volume.[31] If capillary endothelial cells are edematous, the capillary lumen size will diminish, creating an increased resistance to arterial flow. Capillary permeability is usually not directly affected in cytotoxic edema. Major decreases in cerebral function occur with cytotoxic edema, with stupor and coma being common signs.[31] In addition to cytotoxic edema, vasogenic edema develops as a result of disruption of the BBB that includes damage of endothelial cells, degeneration of pericytes, and loss of astrocytes.

Extravasation of blood components and water occurs resulting in increased extracellular fluid accumulation. This is referred to as vasogenic edema.[31] Cerebral white matter is especially vulnerable to vasogenic edema, possibly owing to its low capillary density and blood flow.[29,31] Vasogenic edema displaces cerebral tissue and increases intracranial pressure. Understanding the complex pathophysiological events that take place after TBI is important for development of effective monitoring and treatment strategies.

Spinal Cord Injury

Secondary to trauma, SCI is a dynamic process of which the severity is related to the velocity, degree, and duration of the impact. Blunt injuries to the spinal cord occur under various loading conditions, including flexion, extension, axial load, rotation, and distraction. Forces that produce the primary mechanical insult to the spinal cord in their mildest form result in cord concussion with brief transient neurologic deficits and in their most severe form result in complete and permanent paralysis. Cord concussion with transient neurologic deficits is a result of local axonal depolarization and transient dysfunction, whereas permanent paralysis is a result of primary tissue injury followed by spreading of secondary damage that expands from the injury epicenter.

Primary injury is the initial mechanical damage to the components of the spinal cord that follows acute insult. Blood vessels are broken, axons are disrupted, and neuron and glial cell membranes are damaged. Consequences of primary injury are predominantly visible in the central gray matter. Immediately after injury, the gray matter at the region of impact contains disrupted cells and blood; however, the surrounding white matter, and the gray matter cranial and caudal to the impact region, can appear remarkably intact. The reason for this is not entirely clear but is most likely related to the rich blood supply and increased metabolic requirements for oxygen and glucose of the nerve cell bodies in the gray matter and the biomechanical properties of the myelin ensheathed axons in the surrounding white matter. Ensuing pathophysiological processes involving ischemia, release of chemicals from injured cells, and electrolyte shifts alter the metabolic milieu at the level of the lesion and trigger a secondary injury cascade that substantially compounds initial mechanical damage (Figure 24.1; Table 24.2). These secondary injury processes do not necessarily coincide with the clinical picture, as pathologic changes may progress in severity for weeks to months, even in the face of clinical improvement.

Secondary injury involves both necrotic and programmed cell death, and although mechanisms involved in this are not fully understood, some aspects of this process are well described. Disruption of cellular and subcellular membranes of glia, neurons, and vascular endothelial cells is believed to be the initiator of this autodestructive cascade of events, and it is likely that multiple mechanisms are involved such as ischemia, inflammation, free radical-induced cell death, excitotoxicity, cytoskeletal degradation, and induction of apoptotic pathways. The consequence of secondary injury is enlargement of the area of cell death. The phase of secondary injury is widely studied because this process progresses from minutes to months after injury and is, thus, considered to be a target for therapeutic interventions. Minimizing secondary injury through protection of neural elements that initially survived the mechanical injury would increase the quantity of spared tissue and could lead to reduced functional impairment.

Acute injury results in immediate hemorrhage and cell destruction within the central gray matter. This early, often progressive, hemorrhage is one of the hallmarks of acute SCI. Loss of microcirculation involving predominantly capillaries and venules subsequently spreads over considerable distance cranial and caudal to the site of injury. Furthermore, the cord swells within minutes of injury mainly due to hemorrhage and development of edema. The initial hemorrhage, edema, and hypoperfusion of the gray matter extends centripetally within minutes to hours of injury and results in central necrosis, white matter edema, and eventually, demyelination of axons through secondary injury processes.

Spinal cord ischemia develops over several hours after injury and is considered one of the most important contributors to secondary injury.[32,33] The mechanical disruption of the microvasculature causes petechial hemorrhage and intravascular thrombosis, which in combination with vasospasm of intact vessels and edema can lead to profound local hypoperfusion and ischemia. Cord swelling that exceeds venous blood pressure results in secondary ischemia, and ischemia is further exacerbated by ceasing of autoregulation of spinal cord blood flow and

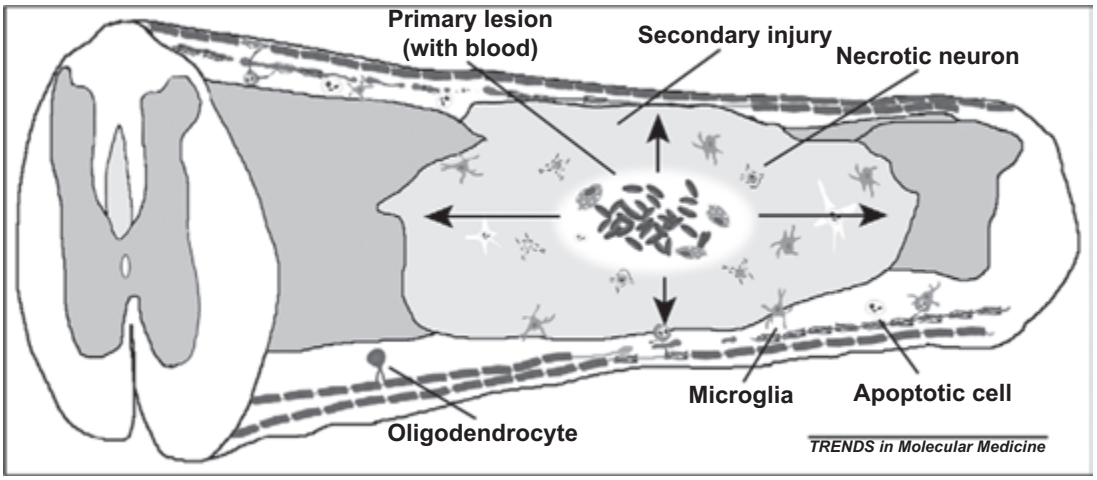


Figure 24.1. Secondary spinal cord injury. Initial trauma to the cord is directed to the central gray matter, where frank destruction occurs. The initial injury is followed by a cascade of biochemical events (secondary injury) that is thought to enlarge the area of cell death through necrosis and apoptosis. Neurons and glial cells at the margins of the expanding lesion represent a target for neuroprotection. When axons in the white matter are damaged, Wallerian degeneration can induce microglial activation and apoptotic cell death of oligodendrocytes long after the initial injury. This later microglial activation represents another potential target for treatments that reduce microglial activation and/or oligodendrocyte apoptosis.

Table 24.2. Characteristics of Primary Injury and Factors that Play a Role in the Cascade of Secondary Injury

	Secondary Injury	
Primary Injury	Cellular/Biochemical	Systemic
Mechanical injury	Vascular (microvasculature, thrombosis, ischemia, and coagulation factors)	Hypoxia
Hemorrhage	Excitotoxicity/elevated intracellular calcium	Hypotension
Diffuse axonal injury	Oxidative stress/free radicals/lipid peroxidation	Hyperglycemia
	Electrolyte shifts	Fever
	Inflammatory cells, mediators, and cytokines	Seizure activity

systemic hypotension. Under normal circumstances, constant local cord hemodynamics are maintained during systolic blood pressure fluctuations approximately between 50 and 130 mmHg,[32,34] but loss of autoregulation after SCI makes the cord vulnerable to systemic arterial pressure. In other species, it has been demonstrated, experimentally, that immediately after initial SCI, a brief period of systemic hypertension is followed by systemic hypotension.[35–38] Furthermore, acutely traumatized

patients can present with systemic hypotension secondary to hypovolemia and/or consequences of loss of sympathetic tone, such as neurogenic shock and bradycardia. SCI can be markedly worsened under ischemic and hypoxic conditions, which is why maintaining normotension after SCI is recommended. Unfortunately during reperfusion conditions, secondary injury may be worsened as a consequence of increase in oxygen-derived free radicals.[39]

During the ischemic hypoxic state, cell metabolism is altered such that a shift occurs from aerobic to anaerobic metabolism, which is a less efficient method of energy production. Anaerobic metabolism results in lactic acid accumulation, causing acidosis in nervous tissue, thus decreasing glucose and oxygen consumption. Furthermore, lactic acid stimulates prostaglandin production, adenosine diphosphate release, platelet aggregation, thromboxane A2 release, vasospasm, vasoconstriction, and the inhibition of neurotransmitter release. In addition, in hypoxic states, the sodium–potassium ATPase-dependent cell pump is inhibited or damaged, resulting in the cell's inability to maintain its electrical polarity. Damage to this pump allows for the accumulation of potassium extracellularly and sodium intracellularly, which contributes to the development of edema.[40]

Free radicals can cause progressive oxidation of fatty acids in cellular membranes (lipid peroxidation) through reactions with their unpaired electrons. Furthermore, oxidative stress can disable key mitochondrial respiratory chain enzymes, alter DNA/RNA and their associated proteins, and inhibit sodium–potassium ATPase. These changes can induce metabolic collapse and necrotic or apoptotic cell death and are considered important during the initial period of hypoperfusion and perhaps even more important during the period of reperfusion. In addition to oxidative stress and membrane damage, NO production and excitatory amino acid-induced calcium entry are considered important mediators of necrotic and apoptotic cell death.[41]

Excitotoxicity refers to the deleterious cellular effects of excess glutamate and aspartate stimulation of ionotropic and metabotropic receptors. Extracellular concentrations of both of these excitatory amino acids are increased after acute SCI, which occurs through release from damaged neurons, decreased uptake by damaged astrocytes, and depolarization-induced release. Ionotropic receptors include the *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainite through which extracellular calcium and sodium can pass down a massive concentration gradient into the cell or, when activated, can result in the release of calcium from intracellular stores. Metabotropic glutamate receptors are coupled to G proteins that act as secondary intracellular messengers to mediate a wide spectrum of cellular functions. Furthermore, elevation of intracellular calcium concentration can occur through direct membrane damage and voltage-gated calcium channels triggered by membrane depolarization. Elevated intracellular calcium concentrations can trigger a multitude of calcium-dependent processes that can lethally alter cellular metabolism, such as activation of lytic enzymes (calpains, phospholipase A2, proteases, and lipoxygenase), generation of free radicals, impairment of mitochondrial function, spasm of vascular smooth muscle, and binding of phosphates with subsequent depletion of cell energy sources. Sodium dysregulation is thought to be important in the pathophysiology of damage to axonal and glial components in the white matter through similar mechanisms that lead to elevated intracellular calcium concentrations.

Controversy exists surrounding the role of inflammation in acute SCI, mainly because the effects of inflammatory cells can be both cytotoxic and protective. After SCI, the injury site is rapidly infiltrated by blood-borne neutrophils, which can secrete lytic enzymes and cytokines. Later, blood-borne macrophages and monocytes, as well as locally activated resident microglia, are recruited—both of which subsequently invade to phagocytose the injured tissue. These and other reactive cells produce cytokines such as tumor necrosis factor (TNF) alpha, interleukins, and interferons, which mediate the inflammatory response and can further damage local tissue and recruit other inflammatory cells.

Among the cytokines involved in secondary SCI, TNF-alpha is perhaps the most extensively studied. It is produced by a range of cell populations, including neutrophils, macrophages and microglia, astrocytes, and T cells, and has been shown to accumulate quickly at the site of SCI. Interestingly, TNF-alpha has been shown to have cytotoxic and neuroprotective properties, which demonstrates the

complexity of the role of inflammation in SCI. Similarly, macrophages traditionally are implicated in furthering tissue destruction,[42] but recently it has been suggested that increasing the number of activated macrophages may have a neuroprotective effect.[32,43,44] It is likely that the quality of macrophages and the characteristics of their environment are important in determining macrophage effector functions.[42] It has been suggested that the early inflammatory phases are deleterious in nature, whereas the later inflammatory events appear to be protective.[32]

Currently, much research is being performed on the role of apoptosis, or programmed cell death, in secondary injury. This slowly spreading form of cell death is induced by the injury and is characterized by apoptotic neurons at the lesion margins and, even later, apoptosis of oligodendrocytes in areas with degenerating axons that were injured at the original lesion site.[41,45] Apoptosis can thus occur at quite remote distances from the point of impact. Oligodendrocytes appear vulnerable to apoptosis, and death of these cells can result in demyelination of otherwise spared axons, thus contributing to the loss of distal neurologic function.

CLINICAL SIGNS AND DIAGNOSIS

Traumatic Brain Injury

Clinical signs associated with head trauma range from inapparent to recumbency with unconsciousness or death. A complete physical examination is very important in head trauma cases, as fractures and other concurrent injuries are not uncommon and require identification and treatment. Physical examination findings as a result of head trauma can include fractures, hemorrhage from the nostrils, mouth, and/or ears, CSF draining from the ear, respiratory distress, cardiac arrhythmias, and hypo- or hypertension.[4,6,8,46]

Hemorrhage from the nose typically presents as dark colored (venous) blood and originates from a paranasal sinus, ethmoid turbinates, or nasal cavity. Occasionally, blood is bright red and then usually originates from larger vessels in the guttural pouches.[4,47] Respiratory distress can occur associated with significant throat swelling after profuse hemorrhage into the guttural pouches. Furthermore, neurogenic pulmonary edema has been reported to occur. The pathophysiology of the development of neurogenic pulmonary edema appears to be associated with a sudden increase in intracranial pressure that triggers an upregulation of sympathetic signal transduction to ensure brain perfusion. Immediate consequences are an increased tonus of venous and arterial vessels and increased myocardial function. However, if systemic vascular resistance increases excessively, left ventricular failure and finally pulmonary edema may result. Additionally, the presence of protein-rich edema fluid suggests altered endothelial permeability within the pulmonary circuit, which is thought to be caused by the acute pressure increase and by neurohumoral mechanisms. The most important CNS structures involved in the development of neurogenic pulmonary edema are the medulla oblongata and the hypothalamus.[48] Acute elevation of intracranial pressure may also result in the Cushing's reflex, which is a hypothalamic response to brain ischemia and is characterized by hypertension and secondary baroreceptor-mediated bradycardia. Furthermore, continued elevation of intracranial pressure and reduction of cerebral blood flow results in increased sympathetic discharge (catecholamines) with subsequent myocardial ischemia and development of cardiac arrhythmias. This is referred to as the brain–heart syndrome.

Life-threatening injuries should be attended to first and then a complete neurologic examination should be performed. Horses may be recumbent and/or intractable following a traumatic incident, and examination and management of these horses can be difficult and dangerous.[46,49] Sedation may be necessary for examination. Although alpha-2 agonists may transiently cause hypertension, which may potentiate intracranial hemorrhage,[15] xylazine has been found to cause a minor decrease in cerebrospinal pressure in normal, conscious horses.[50] It is believed that xylazine is probably a safe sedative to use in horses with head trauma, if the horse's head is not allowed to drop to such a low position that postural effects could lead to physiological increases of intracranial pressure.[5]

The complete neurologic examination should include an assessment of the horse's mentation, cranial nerve function, posture, and ability to coordinate movements as well as its ability to regulate rate and range of motion. Also, reflex and nociceptive testing should be performed to investigate any concurrent SCI. Figure 24.2 provides an outline for localizing the level of brain injury based on the

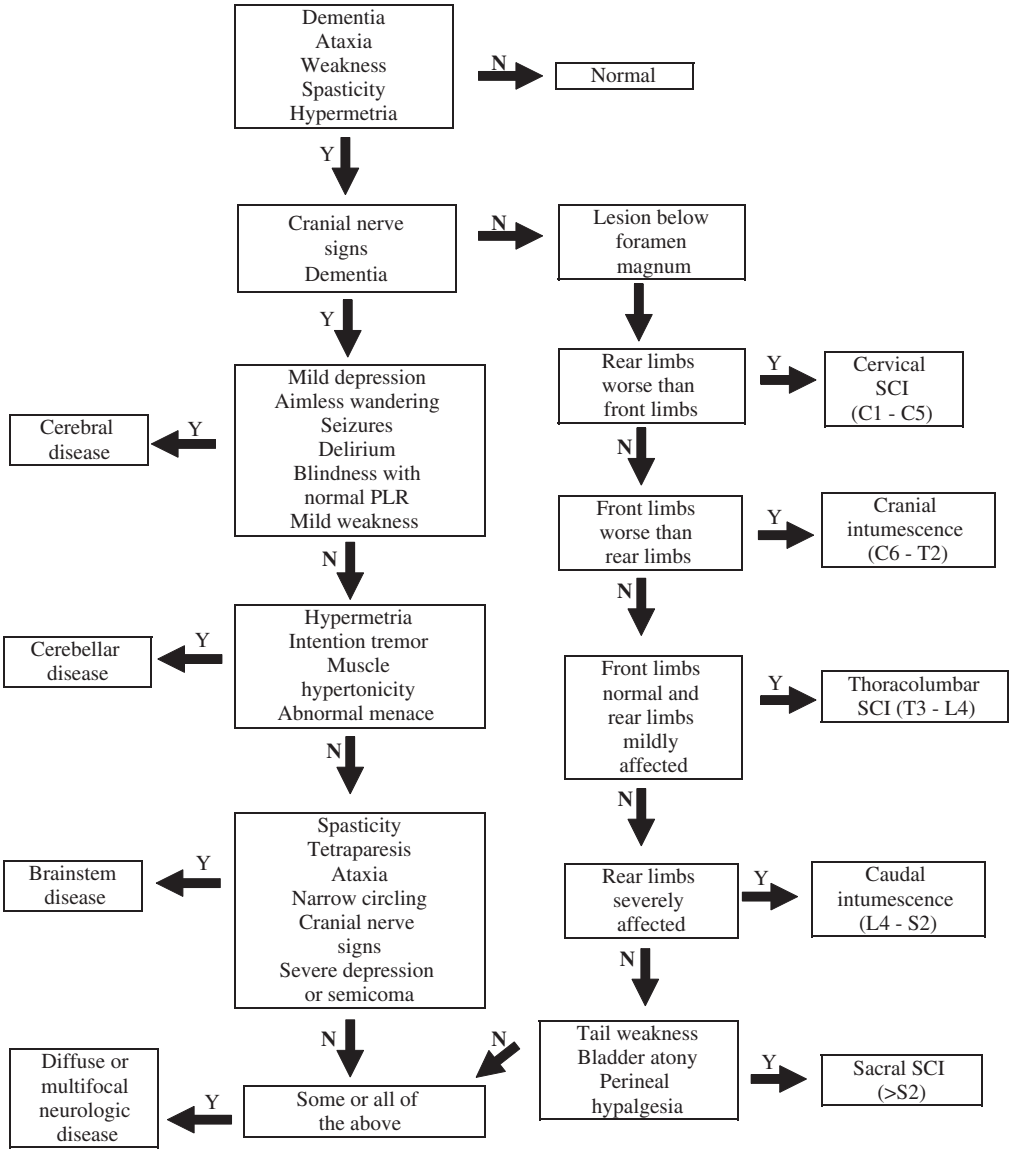


Figure 24.2. Flowchart for localizing a lesion in the nervous system in a recumbent horse. Adapted from: Matthews HK, Nout YS. 2004. "Spinal cord, vertebral, and intracranial trauma." In Equine Internal Medicine, edited by Reed SM, Bayly WM, Sellon DC. St. Louis: Elsevier.

neurologic findings. Serial neurologic examinations, particularly during the first hours, are important for diagnostic purposes and to allow prediction of a more accurate prognosis. Furthermore, serial examinations are important to assess response to therapy.[5,49] Pupil size, symmetry, and response to light should be assessed in all horses, and monitored carefully, particularly in recumbent horses. A change from bilateral pupillary constriction to bilateral dilation with no response to light is a poor prognostic indicator.[5]

The most common neurological syndromes following head trauma are a result of hemorrhage into

the middle and inner ear cavities. Signs are those of central or peripheral vestibular disease and facial nerve damage and include recumbency, head tilt, neck turn, body lean, and circling, all toward the side of the lesion. The ipsilateral eye may be rotated ventrally and laterally, and there may be horizontal or rotary nystagmus with the fast phase away from the lesion.[4,15] Facial paralysis on the same side as the lesion is seen with cranial nerve VII damage. Central vestibular disease is suspected when signs of brainstem disease of more cranial nerve deficits are present. Central vestibular lesions can result in a paradoxic vestibular syndrome, in which the lesion is located on the side opposite to that which is expected from the clinical signs.[4] More serious trauma can lead to alterations of mentation and/or behavior.

The level of consciousness is affected by the degree of damage to the cerebrum and reticular activating system in the brainstem. Immediately after cerebral injury, there is a period of concussion with unconsciousness for various periods of time or even coma. Usually a horse recovers from this in minutes to hours. Comatose horses may have an irregular breathing pattern with periods of either Cheyne–Stokes respiration or hyperventilation. In some horses, seizures can occur after initial concussion; these are typically generalized seizures. Level of mentation and responsiveness to reflexes should be assessed and recorded. Injury to the occipital cortex can result in impairment of vision and menace response of the eye contralateral to the lesion. Pupillary light reflex, however, should remain intact. Injury to the parietal cortex can result in decreased facial sensation on the contralateral side. Another sign of cerebral damage is dementia, or altered behavior, such as walking in circles (toward the side of the lesion), head pressing, hyperexcitability, or aggresion.[4,5,15]

Severe rostral brainstem injuries (mesencephalon) can be associated with coma and depression due to damage to the reticular activating system. Strabismus, asymmetric pupil size, and loss of pupillary light response can be present due to damage to cranial nerve III. Apneustic or erratic breathing reflects a poor prognosis, and bilaterally dilated and unresponsive pupils indicate an irreversible brainstem lesion. These lesions can occur immediately after injury, secondary to herniation of components of the cerebrum or cerebellum or following hemorrhage. Severe brainstem injuries may result in a decorticate posture, characterized by rigid extension of neck, back, and limbs.[4] Injury to caudal parts of the brainstem (pons and medulla) result in dysfunction of multiple cranial nerves in addition to depression and limb ataxia and/or weakness. To make a distinction between a cranial cervical spinal cord and caudal brainstem lesion, careful assessment of the horse's mentation and function of cranial nerves X and XII is important.[4,5]

Signs of cerebellar injury occur infrequently and include intention tremor, broad-based stance, spastic limb movements, and absent menace response with normal vision. If multiple areas of the brain are damaged, this will be reflected in the different clinical signs. Multifocal damage or progression of disease through hemorrhage and/or secondary injury mechanisms is suggested when clinical signs are become more widespread.

Diagnostic tools that are helpful in further defining cranial trauma include radiography, computed tomography (CT), magnetic resonance imaging, endoscopy, electrodiagnostics, and CSF analysis. Radiographs are used to determine the presence and severity of fractures, hemorrhage in cavities, or stylohyoid bone and/or bulla thickening. CT is currently available in many equine clinics. The requirement for general anesthesia and costs are the main disadvantages of using this technique. CT is very sensitive for the detection of bony abnormalities and also provides some information on soft tissues and brain matter.[51–53] Changes seen after TBI include changes in the size, shape, and position of the ventricles, deviation of the falx cerebri, and focal changes in brain opacity.[4] In humans, CT findings may include midline shift and obliteration of sulci and cisterns, for which a grading system exists that can be used in combination with other diagnostics for prognostication purposes.[54] Enhancement of areas of injury or hemorrhage is possible with iodinated contrast agents. Magnetic resonance imaging offers a higher sensitivity for examination of soft tissue structures and has the ability to acquire images in all planes. However, magnetic resonance imaging techniques are not available widespread for equine clinicians yet. Magnetic resonance imaging allows differentiation of gray/white matter, detection of abnormal tissue signals, and mass effect shifts. Furthermore,

magnetic resonance imaging allows documentation of swelling, edema, and hemorrhage.[53] Tremendous advances in neuroimaging are being made that allow determination of blood flow and brain activity (functional magnetic resonance imaging) or imaging of ferritin/hemosiderin that allows closer examination of shear damage (gradient imaging). Determining brain hyperactivity with modern imaging tools could suggest the presence of a concussion, because brain metabolism in that case is increased typically to maintain local homeostasis. The clinical application of these techniques in equine medicine is not likely to be available soon, however.

Upper respiratory endoscopy is an important diagnostic procedure for evaluation of cranial nerve function, stylohyoid bones, retropharyngeal area, and appearance of guttural pouches. Use of electrodiagnostics is typically not indicated immediately after TBI; however, after stabilization or during recovery, these techniques will provide information about certain levels of (dys)function. For example, electroencephalograms are used for assessment of seizure activity, brainstem auditory-evoked response is used for examination of vestibular function, and visual function is examined with visual-evoked potential in combination with electroretinography. CSF analysis may not always be indicated after acute trauma but may be useful for excluding other diseases. Cisternal CSF collection is contraindicated if increased intracranial pressure is suspected because of the possibility of brain herniation through the foramen magnum. Lumbosacral collection is a safer alternative but can be normal despite a traumatic episode, especially in the acute phase, and because the sample is not obtained closest to the lesion, it may not reflect the changes that have occurred. It has been shown that CSF lactate concentrations are increased after trauma in horses.[55]

More invasive diagnostic and monitoring modalities are available (Table 24.3). Methods to measure and monitor intracranial and cerebral perfusion pressures have been described for use in foals[56] and adult horses[57–61]; however, these techniques have thus far not been scientifically evaluated in clinical cases. In human medicine, development of advanced bedside neuromonitoring devices has been an important focus in neurocritical care. The four most important parameters to be determined are intracranial pressure, cerebral blood flow, information on brain metabolism, and functional outcome. Routinely, neurointensivists are able to determine intracranial pressure and cerebral blood flow, but development of other techniques is in progress. For example, some neurointensivists use jugular oxygen saturation (normal: 75–80%, $<$50% considered ischemic), microdialysis, and brain tissue oxygen monitoring techniques to evaluate TBI patients (Table 24.3). The ultimate goal is identifying what combination of parameters is associated with long-term functional outcome.

Microdialysis allows measurement of many biochemical substances, such as those involved in metabolism (e.g., glucose, lactate, pyruvate, glycerol, adenosine, and inosine) or excitatory amino acids (e.g., glutamate) or cytokines (interleukins 6

Table 24.3. Monitoring Techniques that are Currently Being used by Human Neurointensivists and that could be used by Equine Clinicians (Left Column) and Techniques that are Being used only in Certain Specialized Centers for Human Traumatic Brain Injury (TBI) (Right Column)

Monitoring	
Available	Not Readily Available/Experimental
Neurological examination	Cerebral perfusion pressure
Neuroimaging	Cerebral blood flow
Arterial blood pressure	Brain tissue oxygen
Jugular vein oxygen saturation	Microdialysis (glucose, lactate, and pyruvate)
Intracranial pressure	

and 1 beta). Problems associated with this technique are location of catheter placement, focal differences in substance concentrations, and gray/white matter differences in substance concentrations. Current recommendations are to use the microdialysis lactate/pyruvate ratio as the primary marker for secondary ischemia in TBI. Microdialysis glucose, glycerol, and glutamate are additional markers of impending ischemia.[62,63]

Probes that determine brain tissue oxygen tension are placed similarly to those that measure intracranial pressure. They provide a continuous qualitative measure of parenchymal tissue oxygen tension. Although a great deal remains to be investigated with regard to both of those techniques, it has been shown that low oxygen tensions are associated with ischemia or hypometabolism. Brain oxygen monitoring, however, is not strictly a method of determining ischemia because level of metabolism also is a determinant for oxygen tensions. It appears that use of multimodality monitoring techniques, in which complimentary regional neuromonitoring tools that may measure tissue pH, cerebral blood flow, or biochemical metabolites should be part of an overall strategy.[64]

Spinal Cord Injury

Clinical signs resulting from trauma reflect the extent and location of the injury. Neurologic signs are usually observed immediately after the accident but may occur weeks to months after the initial insult because of delayed damage to the spinal cord caused by instability, arthritis, or bony callus formation at the site of impact. Clinical signs depend on the neuroanatomical location of injury and range from inapparent to severe incapacitating tetraparesis or tetraplegia. Lesions causing recumbency are mostly found in the caudal cervical or thoracic spinal cord, whereas lesions of nonrecumbent horses are mostly found further cranial in the cervical spinal cord or in the lumbosacral cord.[1]

Initial evaluation of the patient should be directed toward stabilization and correction of any life-threatening problems such as airway obstruction, hemorrhage, cardiovascular collapse, and pneumothorax. In addition, major long-bone fractures must be identified, as these may be the limiting factor for survival of the horse. All affected horses may be nervous or agitated as a result of pain and the inability to stand. A systematic neurologic evaluation should then be performed to localize the site of injury (Figure 24.2).[7,46,49,65] In recumbent horses, the use of a sling to assist standing may be a valuable diagnostic tool for localizing the site of injury and for assessing progression of disease and prognosis.[49,65]

In animals, SCI usually occurs as a solitary lesion, and the level of the lesion is readily diagnosed by neurologic examination.[66] Depression or loss of a segmental spinal reflex implies damage to the afferent, efferent, or connecting pathways of the reflex arc. However, after acute SCI, a phase of spinal shock can occur in which there is profound depression in segmental spinal reflexes caudal to the level of the lesion, even though reflex arcs are physically intact.[66–68] Spinal shock occurs in all species, however, appears to be of less clinical significance in lower mammals when compared with primates.[66,69] Spinal shock has a much shorter duration in dogs, cats, and rabbits compared with humans. Anatomic differences (localization, significance, and projection pattern) of the tracts for descending motor control (corticospinal tract) and subsequent differences with respect to responses to injury (tracts damaged and regeneration/plasticity within the cord) in lower mammals versus humans contribute to the more rapid recovery from spinal shock in nonprimates.[66] Another syndrome that occurs infrequently and is short lived in the horse is Schiff–Sherrington syndrome, in which extensor hypertonus is present in otherwise normal thoracic limbs in patients with a severe cranial thoracic lesion.[69]

Cord injury typically results in damage that is worse in the large myelinated motor and proprioceptive fibers compared with the smaller or nonmyelinated nociceptive fibers. Therefore, ataxia and loss of proprioception and motor function will occur before the loss of deep pain.[7] Flaccid paralysis with hypo- or areflexia, muscular hypotonia, and neurogenic muscle atrophy are characteristic of a lower motor neuron lesion. Clinical signs resulting from an upper motor neuron spinal cord lesion include loss of voluntary motor function, whereas muscle tone may be increased and spinal reflexes may be normal to hyperactive. Development of hyperreflexia occurs over time and is thought to be a result of removal of supraspinal inhibitory input, sprouting of fibers under the influence of altered growth factor concentrations, and increased synaptic excitability that occurs within the spinal cord distal to the level of the lesion.[70–74]

In horses, lesions in the C1–T2 region are most common and result in various degrees of tetraparesis to recumbency. Thoracolumbar SCI can result in paraparesis to recumbency, and horses may dog-sit. Sacral cord damage can result in fecal and urinary incontinence, loss of use of tail and anus, muscle atrophy, and mild deficits of pelvic limb function. Sacrococcygeal spinal cord injury can produce hypalgesia, hypotonia and hyporeflexia of the perineum, tail, and anus, or total analgesia and paralysis of those structures. In addition to these clinical signs, loss of sensation can occur distal to the level of SCI. Furthermore, diffuse sweating can be seen as a result of loss of supraspinal input to the preganglionic cell bodies of the sympathetic system in the thoracolumbar intermediate gray. Patchy sweating can be seen with damage to specific preganglionic or postganglionic nerve fibers.[7,69]

Ancillary diagnostics that may aid in the diagnosis or localization of SCI include radiography, myelography, CT, magnetic resonance imaging, nuclear scintigraphy, CSF analysis, nerve conduction velocities, electromyography, and transcranial magnetic stimulation. Radiography may demonstrate fractures, luxations, subluxations, and vertebral compression. As presented above, CT or radiography are the diagnostic aids of choice to evaluate skeletal injury, whereas magnetic resonance imaging is more sensitive for evaluation of soft tissue structures such as the spinal cord and ligaments. With respect to imaging, the vertebral column with CT and magnetic resonance imaging devices, however, the size of the horse as well as equipment aperture size and costs limit its use to investigations of the cervical and cranial thoracic spinal cord. Myelography may be required to confirm spinal cord compression and can be used at the level of the cervical, cranial thoracic, and sacral–coccygeal spinal cord. Nuclear scintigraphy can be useful in diagnosing nondisplaced or occult fractures and soft tissue lesions. Common CSF abnormalities following SCI include xanthochromia and mild-to-moderate increased total protein concentrations.[7] CSF analysis may be normal, especially in very acute or chronic cases. Nerve conduction velocity and electromyographic studies evaluate the lower motor neuron and aid in lesion localization. Electromyographic changes, however, may not develop until 4–5 days following nerve damage.[75] Transcranial magnetic stimulation allows detection of functional lesions in descending motor tracts through recording of magnetic motor-evoked potentials. This method has recently been validated and used to distinguish motor tract disorders from other causes of recumbency in clinical cases.[76–78]

NEUROCRITICAL CARE AND PROGNOSIS

Traumatic Brain Injury

Based on the pathophysiology of events that occur after TBI, it is likely that single drug intervention would not be effective. However, most research studies and pharmaceutical trials follow this single drug intervention approach. Treatment of TBI is aimed at optimizing delivery of oxygen and substrates to brain tissue to salvage brain tissue that is undamaged or reversibly damaged. This requires optimizing cerebral blood flow, that is, optimizing mean arterial blood pressure and hemoglobin concentration, and ensuring intracranial pressure is not elevated. Emergency surgical treatment (although not commonly performed) is warranted in open cranial fractures and in the face of deterioration despite medical therapy. Once the patient is stabilized, repair of less life-threatening fractures can be considered. Furthermore, research is focused on secondary injury and pharmacologic intervention that could affect pathways involved in this delayed cell death. Evaluation of potential treatment strategies has recently been reviewed.[79]

Table 24.4 summarizes methods that are currently used in human neurocritical care units to reduce elevated intracranial pressure. Treatment to reduce intracranial pressure is commenced at pressures of 20–25 mm Hg. In the acute setting, human neurointensivists perform a neurologic examination and hyperventilate patients at risk for having elevated

Table 24.4. Methods that are Used to Reduce Intracranial Pressure, Listed from Least Aggressive to Most Aggressive

Hyperventilation
Cerebrospinal fluid drainage
Hyperosmolar treatment
Sedation
Barbiturates
Decompressive craniectomy

intracranial pressures while awaiting brain imaging. Hyperventilation reduces the partial pressure of carbon dioxide in blood and subsequently leads to cerebral vasoconstriction. Reduced cerebral blood volume reduces intracranial pressure. However, cerebral vasoconstriction may lead to reduction of cerebral blood flow to ischemic levels. It is currently recommended that hyperventilation to reduce intracranial pressure is only used if hyperemia is a contributor to elevated intracranial pressure or in combination with intensive neuromonitoring and for limited duration. Hyperventilation could be considered in cases of increased intracranial pressure in horses. Proper hyperventilation requires monitoring of arterial blood gases and may require use of neuromuscular blockers if the horse is not comatose and is resisting ventilation. CSF drainage is commonly used in people to reduce intracranial pressure, however, is considered a therapeutic treatment only if there is CSF outflow obstruction. If these methods are ineffective, repeat imaging is pursued to investigate the presence of mass lesions before medical treatments are commenced such as administration of hyperosmolar substances and induction of barbiturate coma. Hyperosmolar treatment is commonly used in horses with neurologic signs attributable to TBI. This is discussed later in this section.

Mean arterial blood pressure should be maintained within normal limits (in humans: >90 mm Hg). Unlike SCI in which sympathetic outflow is often disrupted and pressor therapy indicated, this is not common with TBI and the goal is to maintain normal mean arterial blood pressure and euvolemia by isotonic crystalloid fluid therapy. Interestingly, in a study comparing treatment guided by intracranial pressure (<20 mm Hg) with treatment guided by cerebral perfusion pressure (>70 mm Hg), the incidence of acute respiratory distress syndrome was significantly higher in the latter group and there were no functional outcome differences between the two treatment regimens.[80] A recent study suggests individual tailoring of these treatment strategies depending on the relationship of mean arterial and intracranial pressure responses to treatment.[81] Crystalloid fluids (0.9% NaCl) are recommended as fluid therapy of choice, particularly in light of findings of the serum versus albumin fluid evaluation (SAFE) study,[82] that determined no difference in outcomes between administering albumin and normal saline in the intensive care unit and in which subgroup analysis demonstrated an increased mortality in TBI patients who were treated with albumin. However, isotonic crystalloid fluids administered in typical shock doses of 40–90 ml/kg/h may produce worsening of cerebral edema and increased intracranial pressure.[83] Comparison of isotonic crystalloid fluids with hypertonic saline solutions has shown hypertonic saline to be the fluid of choice for fluid support of head trauma patients in shock.[84] Hypertonic saline is associated with significant decreases in intracranial pressure and cerebral water content compared with isotonic fluid treatment. Furthermore, hypertonic saline has positive effects on cerebral blood flow, oxygen consumption, and inflammatory response at a cellular level.[85] Hypertonic saline can be administered to horses with head trauma that are in shock as 5 or 7% NaCl solutions (4–6 ml/kg, IV) over 15 min. Isotonic fluids can then be used for maintenance if needed. Contraindications to the use of hypertonic saline include dehydration, ongoing intracerebral hemorrhage, hypernatremia, renal failure, hyperkalemic periodic paralysis, and hypothermia. Systemic side effects include coagulopathies, excessive intravascular volume, and electrolyte abnormalities. Monitoring central venous pressure and maintaining it within normal limits (5–7 cmH_2O) as well as monitoring serum sodium and potassium concentrations is therefore important if hypertonic saline is used frequently.[84]

Blood transfusion may be indicated in situations of severe hemorrhage. Although hemoglobin deficiency adversely affects oxygen delivery to tissues and guidelines for traumatic injury traditionally have advocated aggressive treatment of anemia in TBI, a recent human study has demonstrated that, similar to other critical care patients, blood transfusions negatively affected outcome in TBI patients.[86] The threshold for transfusion should thus be no different than in other patients.

The use of carbohydrate-containing intravenous solutions should be avoided early in the treatment of head trauma patients. Glucose suppresses ketogenesis and may increase lactic acid production by the traumatized brain, limiting the availability of nonglycolytic energy substrates.[87] Furthermore, carbon dioxide liberated from glucose metabolism could cause vasodilation and worsening of cerebral edema. It has been well established that maintaining blood glucose concentrations at 80–110 mg/dl through intensive insulin therapy reduces morbidity and

mortality in human critical care patients.[88] However, neurointensivists have shown that intensive insulin therapy increases markers of cellular distress in the brain and suggest that systemic glucose concentrations of 80–110 mg/dl are too low in TBI and may lead to cerebral hypoglycemia.[89] Current recommendations are to maintain blood glucose concentrations at 120–140 mg/dl in TBI.

Treatment with antiinflammatories is likely the most commonly used treatment in equine TBI. Indications for use of antiinflammatory treatment are to combat the inflammatory pathways of secondary injury mechanisms (cytokine release and free radicals), improve comfort level, and reduce fever. Fever occurs extremely common after TBI, and it has been well documented in animal models and in people to negatively affect outcome after TBI, for example, by augmenting secondary injury mechanisms.[90,91] It is proposed that a proactive approach should be taken toward reducing fever. In fact, hypothermia has been shown to be neuroprotective. Hypothermia results in decreased cellular metabolism and has been proven efficacious in treatment of TBI in experimental and clinical settings.[92] The neuroprotective effects include reduced release of excitotoxins, reduction of free radical and inflammatory mediator formation, and reduction of BBB disruption. However, long-term benefits and improved functional outcome have not been adequately demonstrated.[93,94] Commonly used antiinflammatory compounds in equine practice include corticosteroids, nonsteroidal antiinflammatories, dimethylsulfoxide (DMSO), and vitamin E.

Controlling seizures is very important after TBI, because seizure activity increases cerebral metabolic rate and promotes secondary injury. It is not unusual for horses sustaining cranial trauma to develop seizures. Diazepam, midazolam, phenobarbital, or pentobarbital are drugs that can be used for to control seizures. Intractable seizures may necessitate general anesthesia. Agents useful for general anesthesia include guaifenesin, chloral hydrate, barbiturates, and gas anesthesia. Ketamine is not recommended as part of a balanced anesthesia regimen as it increases cerebral blood flow and intracranial pressure. Treatment and management of horses with seizures is further discussed in Section 2, Chapter 6.

Barbiturate treatment or coma may decrease cerebral metabolism, thereby providing a protection against cerebral ischemia. Barbiturates may also limit lipid peroxidation. However, the actual benefits of barbiturate use on neurologic outcome remain controversial. The effects of barbiturates on lowering intracranial pressure are enhanced by concurrent hyperventilation. An exact dosage regimen for barbiturate treatment in horses has not been investigated, but 5–10 mg/kg intravenous to effect is reported to be useful. The major side effect of barbiturates is hypotension, especially if mannitol and furosemide have been administered, so they must be used with caution and adequate blood pressure monitoring. Barbiturates should be reserved for those cases where elevated intracranial pressure is refractory to other treatments. Other methods to lower intracranial pressure include elevation of the head by 30 degrees if no cervical fractures are present[95] and decompressive craniectomy. Rationale for use of the latter is comparison of the effect of a durotomy for compartment syndrome of the brain with that of a fasciotomy in muscle compartment syndrome.[96,97] This technique has been used in normal dogs and was effective at reducing intracranial pressure.[98]

Furosemide has been found effective in decreasing intracranial pressure in an experimental setting.[99] A 1 mg/kg IV bolus was administered at 5-h intervals with a constant infusion of 0.5 mg/kg/h for 4 h, beginning 1 h after the initial bolus. Normal hydration status is required before furosemide is administered. Furosemide may also be used concurrently with mannitol to increase the duration of intracranial pressure reduction provided by mannitol and to diminish the potential for rebound increase in intracranial pressure. Hyperosmolar therapy forms the mainstay of treatment for elevated intracranial pressure.

Mannitol has been the primary osmotherapeutic drug for the last four decades. Mannitol induces changes in blood rheology and increases cardiac output, leading to improved cerebral perfusion pressure and cerebral oxygenation. Improved cerebral oxygenation induces cerebral artery vasoconstriction and subsequent reduction in cerebral blood volume and intracranial pressure. Mild dehydration after osmotherapy is desirable and may improve cerebral edema; however, severe dehydration can lead to hyperosmolality and renal failure. Mannitol also decreases CSF production by up to 50%, which can lead to a prolonged decrease in intracranial pressure.[84] In horses, 20% mannitol can be administered at 0.25–2.0 mg/kg intravenously over 20 min.

Horses receiving osmotic diuretics should be adequately hydrated. The use of osmotic substances is warranted in any horse with worsening mental status, abnormal pupillary size or inequality indicating transtentorial herniation, or development of paresis. Although mannitol is very effective in reducing intracranial pressure, there are several limitations to its use. Hyperosmolality can be associated with renal and CNS effects. Furthermore, administration of multiple doses of mannitol may lead to intravascular dehydration, hypotension, and reduction of cerebral blood flow. Therefore, current research is focused on the use of substitutes for mannitol, of which the most promising is hypertonic saline.

Hypertonic saline has many beneficial effects in TBI. The permeability of the BBB to sodium is low. Hypertonic saline produces an osmotic gradient between the intravascular and the interstitial/intracellular compartments, leading to shrinkage of brain tissue and subsequent reduction of intracranial pressure. The reflection coefficient of NaCl is more than that of mannitol, making it potentially a more effective osmotic drug. As described above, hypertonic saline augments volume resuscitation and increases circulating blood volume, mean arterial blood pressure, and cerebral perfusion pressure. Other beneficial effects include restoration of neuronal membrane potential, maintenance of BBB integrity, and modulation of the inflammatory response by reducing adhesion of leukocytes to endothelium.[84,100] Hypertonic saline typically is used as 3, 5, or 7.5% solutions, but a recent study showed beneficial effects of using small-volume 23.4% hypertonic saline to reduce intracranial pressure.[101]

Animal studies support the use of hypertonic saline in TBI, but definitive human trials with mortality as end point in brain trauma are lacking. Nevertheless, hypertonic saline osmotherapy should be considered a therapeutic adjunct to the multimodal medical management of TBI. An example for an approach to its use for reducing intracranial pressure in humans is intravenous administration of a 4-ml/kg bolus of 3% hypertonic saline that is repeated until intracranial pressure is normalized or until a sodium concentration of 155 mmol/l is achieved. The serum sodium concentration is maintained at this level until intracranial pressure is stabilized and then gradually allowed to decrease. If intracranial pressure is still elevated after 3–4 days, furosemide is used in an effort to mobilize tissue sodium.[84]

Antibiotic treatment is usually warranted in cases of head trauma, especially when fractures are present. The presence of hemorrhage increases the possibility of septic meningitis. Antibiotic choice should be based on culture and sensitivity testing. Common choices for broad-spectrum coverage include trimethoprim-sulfamethoxazole and penicillin in combination with gentamicin. Although aminoglycosides do not penetrate the intact BBB, their use in CNS trauma may help to minimize the possibility of CNS infection from necrotic or contaminated tissue. Appropriate monitoring of aminoglycoside toxicity should be undertaken with their use. Owing to disruption of the BBB, other antimicrobials probably penetrate into the CNS, and therefore their use may also be effective. The use of antibiotics in CNS infection is further discussed in Section 1, Chapter 4.

Nutritional support plays a role in the outcome following neurologic injury. In humans, it has been found that neurologic recovery from head injury occurs faster in patients receiving early adequate nutritional support.[102] If the horse is able to eat, and the gastrointestinal tract is functioning normally, water and good-quality hay should be available at all times. Small amounts of grain should be fed three to four times a day to boost caloric intake. The amount of grain fed should be based on the horse's condition and ability to tolerate grain feeding. Horses with a poor appetite or those unable to swallow may have to be tube-fed using a gruel of alfalfa and complete feed pellets.[49] Horses in which enteral feeding is not possible are candidates for total parenteral nutrition. Additionally, the use of thiamine may be of benefit in treating head injuries because thiamine aids in metabolism of lactic acid and is a necessary coenzyme in brain energy pathways.

The prognosis for cranial trauma is dependent on severity of the insult and early treatment and is gauged by response to treatment. An early prognosis based on initial findings is important to establish for owners and thus can influence clinical decisions. However, in a study performed in human TBI patients, even with sophisticated clinical and radiological technologies, it was not possible to predict outcome on the first day after the accident with sufficient accuracy to guide early management.[103] Here again, it is important to highlight the value of repeated neurologic evaluations. In general, basilar fractures and severe brainstem injuries carry a grave

prognosis.[8] Recumbency, tetraparesis, and severe dementia carry a poor-to-grave prognosis.[6] Time, good nursing care, and adequate nutritional support, especially in the recumbent horse, are vital for a positive outcome.

Spinal Cord Injury

Treatment to reverse primary SCI does not currently exist, and it is the assortment of pathophysiological processes that occur during the period of secondary injury that are considered the target for pharmaceutical intervention. The period of secondary injury can be divided into three therapeutic windows.[104] The first 48 h after acute SCI are dominated by the vascular and biochemical changes that occur within the spinal cord. The second period is a result of the effects of inflammatory cells that occurs within hours of injury and peaks around 4 days after injury. The third period occurs approximately 1 week after injury and is characterized by axonal regeneration and lesion repair. The goals of treatment are to stop the cascade of cellular events initiated by the traumatic insult, to protect undamaged neural tissue, and to promote regeneration. Surgical intervention is warranted when there is need for stabilization, or evidence of a compressive lesion, however, is not a routine practice. The use of medical treatment to stabilize the patient should always be instituted before surgery is performed.

Acute SCI often results in impaired cardiopulmonary function such as impaired ventilation, bradycardia, and hypotension. This is particularly the case in lesions cranial to C5 (respiratory center affected) and cranial to T2 (origin of sympathetic outflow—thoracolumbar spinal cord). Systemic hypotension may exacerbate spinal cord hypoperfusion and ischemia, and maintaining systemic blood pressure has been shown to improve spinal cord perfusion. Volume resuscitation is clearly indicated in shock and for restitution of tissue perfusion. The current recommendation is to maintain euvolemic normotension, and because of sympathetic outflow disruption after cranial SCI, pressor therapy is commonly indicated in the treatment regimen. Maintaining normal mean arterial blood pressure is also important to consider during stabilization of the acutely injured horse and is particularly important when horses are placed under general anesthesia for various diagnostic/therapeutic procedures.

Similar to TBI, SCI has a complex multifactorial pathophysiology and likely requires a combinational treatment intervention for successful outcome. Many agents, which could target different aspects of the secondary injury mechanisms, have been investigated for use in SCI and have been reviewed in many recent publications.[32,105,106] Until now, only methylprednisolone sodium succinate (MPSS) was shown to be efficacious in both animals and humans[107–112]; however, based on conflicting reports and small neurologic improvements, many reviews of the data have been published expressing concern with regard to the true beneficial effect of MPSS in acute SCI.[113–116] MPSS is a synthetic glucocorticoid with 4 times more antiinflammatory activity and 0.8 times less mineralocorticoid action compared with cortisol.[117] Beneficial effects of MPSS on neural tissue include inhibition of lipid peroxidation, eicosanoid formation, and lipid hydrolysis, including arachidonic acid release, maintenance of tissue blood flow and aerobic energy metabolism, improved elimination of intracellular calcium accumulation, reduced neurofilament degradation, and improved neuronal excitability and synaptic transmission. MPSS was selected for human clinical trials rather than dexamethasone because the succinate radical has been shown to cross cell membranes more rapidly than other radicals.[110]

In 1984, the first National Acute Spinal Cord Injury Study (NASCIS I) results demonstrated no significant difference between the effects of MPSS compared with methylprednisolone on outcomes of acute SCI patients.[118] However, results from the NASCIS II trial were more encouraging.[110,119] The results of this multicenter randomized, double-blind, placebo-controlled study in humans compared the effects of MPSS, naloxone, and a placebo on the neurologic outcome of acute SCI patients. MPSS was administered as a 30-mg/kg bolus followed by infusion at 5.4 mg/kg/h for 23 h. Naloxone was administered as a 5.4-mg/kg bolus followed by infusion at 4 mg/kg/h for 23 h. In 1 year, the MPSS group had significant improvement in motor function compared with the other groups, and there was no difference is incidence of complications between the groups.[110] The investigators concluded that high-dose MPSS treatment within 8 h of SCI improved neurologic recovery, and the use of naloxone in SCI was not recommended.[110,119] The dose of MPSS used exceeds that necessary for activation of steroid receptors, suggesting that MPSS acts through mechanisms that are unrelated to steroid receptors, and

apparently, it is the cell membrane antilipid peroxidation effect of MPSS that is most beneficial.[110,119]

In a fifth trial of MPSS (NASCIS III), using essentially the same protocol for drug administration and neurologic assessment as NASCIS II, no significant benefit was found when the NASCIS II regimen of 24-h therapy was extended to 48 h.[112,118] In addition, the NASCIS II and III studies have received intense criticism on several important methodological, scientific, and statistical issues that have been reviewed elsewhere.[116] Moreover, others have not been able to reproduce results obtained from NASCIS II and III.[116] Although there has been no report on increased incidence of adverse effects after MPSS treatment in humans, a recent report in animals has shown that MPSS administration according to the doses recommended in the NASCIS II/III studies include lymphocytopenia, intestinal necrosis, and eosinophilic pulmonary infiltrates.[120] It is suggested that a multinational study should be undertaken to review the current recommendation of MPSS administration.[116] The usefulness of high-dose MPSS treatment of spinal cord trauma in the horse remains to be investigated.

In horses, corticosteroids, alone or in combination with other drugs, are likely the most commonly used drugs for acute CNS trauma. Reported dosages of dexamethasone for horses range from 0.1 to 0.25 mg/kg intravenously every 6–24 h for 24–48 h. A favorable response is expected within 4–8 h after administration. Horses on corticosteroid therapy should be monitored closely for the development of laminitis. Other complications such as fungal or rhodococcal pneumonia have also been seen in such patients. If improvement in clinical signs is observed, the horse may be placed on oral prednisolone therapy (0.5–1.0 mg/kg tapered over 3–5 days) to decrease the risk of laminitis. The neuroprotective effect of corticosteroids is thought primarily to be mediated by free radical scavenging, but may include decreased catecholamines and glutamate, and decreased apoptosis-related cell death.[121] Other potential beneficial effects of corticosteroids include reduction in the spread of morphologic damage, prevention of the loss of axonal conduction and reflex activity, preservation of vascular membrane integrity, and stabilization of white matter neuronal cell membranes in the presence of central hemorrhagic lesions.[40] Furthermore, their antiinflammatory properties may be useful in reducing edema and fibrin deposition as well as their ability to reverse sodium and potassium imbalance due to edema and necrosis. Another beneficial effect of corticosteroids is maintenance of normal blood glucose concentrations while maintaining electrolyte balance.[40]

As mentioned for TBI, the use of nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine and phenylbutazone may decrease the inflammation associated with a traumatic episode and may be beneficial in maintaining a normal rectal temperature. These compounds work by inhibiting cyclooxygenase, which converts arachidonic acid to inflammatory mediators (endoperoxides). In addition, the potential beneficial properties of DMSO, 1 g/kg intravenously as a 10–20% solution for three consecutive days followed by three treatments every other day, likely warrant inclusion of this drug in the treatment of CNS trauma.[5,6] Pharmacokinetic evaluation of DMSO in horses indicate that daily dosing twice is necessary to maintain adequate blood concentration.[122] Reported benefits of DMSO include increased brain and spinal cord blood flow, decreased brain and spinal cord edema, increased vasodilating PGE1, decreased platelet aggregation, decreased PGE2 and PGF2, protection of cell membranes, and trapping of hydroxyl radicals.[40] The exact mechanism of DMSO remains unknown, and this treatment remains controversial as some researchers have found no positive effects on neurologic outcome from the use of DMSO.[123] Although the free radical scavengers vitamin E and selenium have been shown to be beneficial in SCI, these antioxidants do not appear useful in the acute management because of the length of time required to achieve therapeutic concentrations in the CNS.[104]

Similar to TBI, antibiotics are not always necessary in the treatment of vertebral or spinal cord trauma; however, they are indicated in treating open fractures and secondary complications associated with a recumbent horse, such as pneumonia and decubital sores.

Physical therapy is important in the rehabilitative process in spine-injured horses. Controlled exercise allows the unaffected parts of the nervous system to compensate for the affected parts by increasing strength and conscious proprioception. Exercise is especially helpful in improving weakness, ataxia, spasticity, and hypermetria. In recumbent horses, massage, therapeutic ultrasound, and hydrotherapy of affected muscle groups for 10–15 min at least

twice a day are important. These measures help combat necrosis and muscle atrophy of the horse's dependent muscle groups. Passive flexion and extension of all limbs is helpful in maintaining full range of motion in recumbent horses. Furthermore, experimental studies have shown that exercise enhances functional recovery after SCI.[124]

Much of the current research is focused on regeneration of spinal cord after injury, including effects of cellular transplantation strategies. Similar to what has been mentioned earlier for the pharmaceutical intervention in this disease, a transplantation regimen likely will require development of a multimodal intervention strategy. Targets that will need to be included in such a strategy include treatments to alter the lesion environment and optimize its receptiveness for implantation of a transplant that will be able to survive and develop over time. This likely will require the addition of growth factors and/or other substances to drive cells to specific lineages (neuronal/glial) or increase their ability to secrete required biological products. Current reviews regarding these strategies are available.[125–129]

Prognosis is based on response to therapy and is directly related to the time from injury to the institution of treatment. Horses that show rapid neurologic improvement have a fair-to-good prognosis. Recumbent horses or horses suffering from fractures or luxations have a guarded-to-poor prognosis. Horses that have lost deep pain sensation have a functional or anatomical spinal cord transection and have a grave prognosis. The longer the time from loss of deep pain to treatment, the poorer the prognosis. Partial or complete recovery of horses with spinal cord trauma may take weeks to months, so time and nursing care are required.

REFERENCES

1. Feige K, Fürst A, Kaser-Hotz B, Ossent P. 2000. Traumatic injury to the central nervous system in horses: occurrence, diagnosis and outcome. *Equine Vet Educ* 12:220–4.
2. Tyler CM, Begg AP, Hutchins DR, *et al*. 1993. A survey of neurological diseases in horses. *Aust Vet J* 70:445–9.
3. Johnson PJ, Kellam LL. 2001. The vestibular system. Part II: differential diagnosis. *Equine Vet Educ* 3:185–94.
4. MacKay RJ. 2004. Brain injury after head trauma: pathophysiology, diagnosis, and treatment. *Vet Clin North Am Equine Pract* 20:199–216.
5. Reed SM. 1993. Management of head trauma in horses. *Comp Cont Educ Pract Vet* 15:270–3.
6. Reed SM. 1987. Intracranial trauma. In *Current Therapy in Equine Medicine*, edited by Robinson NE, 377–80. Philadelphia:W.B. Saunders Co.
7. Reed SM. 1994. Medical and surgical emergencies of the nervous system of horses: diagnosis, treatment, and sequelae. *Vet Clin North Am Equine Pract* 10:703–15.
8. Stick JA, Wilson J, Kunze D. 1980. Basilar skull fractures in three horses. *J Am Vet Med Assoc* 176:228.
9. Ramirez O, Jorgensen JS, Thrall DE. 1998. Imaging basilar skull fractures in the horse: a review. *Vet Radiol Ultrasound* 39:391–5.
10. Martin L, Kaswan R, Chapman W. 1986. Four cases of traumatic optic nerve blindness in the horse. *Equine Vet J* 18:133–7.
11. Walker AM, Sellon DC, Cornelisse CJ, *et al*. 2002. Temporohyoid osteoarthropathy in 33 horses (1993-2000). *J Vet Intern Med* 16:697–703.
12. Newton SA, Knottenbelt DC. 1999. Vestibular disease in two horses: a case of mycotic otitis media and a case of temporohyoid osteoarthropathy. *Vet Rec* 145:142–4.
13. Blythe LL. 1997. Otitis media and interna and temporohyoid osteoarthropathy. *Vet Clin North Am Equine Pract* 13:21–42.
14. Blythe LL, Watrous BJ, Schmitz JA, *et al*. 1984. Vestibular syndrome associated with temporohyoid joint fusion and temporal bone fracture in three horses. *J Am Vet Med Assoc* 185:775–81.
15. Mayhew IG. 1996. Equine neurology and nutrition. *AEV A Bain-Fallon Memorial Lectures*, 22–26 July, Glenelg, Australia.
16. Pinchbeck G, Murphy D. 2001. Cervical vertebral fracture in three foals. *Equine Vet Educ* 3:24–8.
17. Rashmir-Raven A, DeBowes RM, Hudson L, *et al*. 1991. Vertebral fracture and paraplegia in a foal. *Prog Vet Neurol* 2:197–202.
18. Collatos C, Allen D, Chambers J, *et al*. 1991. Surgical treatment of sacral fracture in a horse. *J Am Vet Med Assoc* 198:877–9.
19. Haussler KK, Stover SM. 1998. Stress fractures of the vertebral lamina and pelvis in thoroughbred racehorses. *Equine Vet J* 30:374–81.
20. Tutko JM, Sellon DC, Burns GA, *et al*. 2002. Cranial coccygeal vertebral fractures in horses: 12 cases. *Equine Vet Educ* 4:250–4.
21. Wagner PC, Long GG, Chatburn CC, *et al*. 1977. Traumatic injury of the cauda equina in the horse: a case report. *Equine Med Surg* 1:282–5.
22. Jeffcott LB. 1980. Disorders of the thoracolumbar spine of the horse–a survey of 443 cases. *Vet J* 12:197.

23. Smith DH, Chen XH, Xu BN, *et al*. 1997. Characterization of diffuse axonal pathology and selective hippocampal damage following inertial brain trauma in the pig. *J Neuropathol Exp Neurol* 56:822–34.
24. Gennarelli TA. 1993. Mechanisms of brain injury. *J Emerg Med* 11(Suppl. 1):5–11.
25. Povlishock JT. 1992. Traumatically induced axonal injury: pathogenesis and pathobiological implications. *Brain Pathol* 2:1–12.
26. Andrews PJ, Citerio G. 2004. Intracranial pressure. Part one: historical overview and basic concepts. *Intensive Care Med* 30:1730–3.
27. Steiner LA, Andrews PJ. 2006. Monitoring the injured brain: ICP and CBF. *Br J Anaesth* 97:26–38.
28. Narayan RK, Greenberg RP, Miller JD, *et al*. 1981. Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. *J Neurosurg* 54:751–62.
29. Golding EM. 2002. Sequelae following traumatic brain injury. The cerebrovascular perspective. *Brain Res Brain Res Rev* 38:377–88.
30. Verweij BH, Muizelaar JP, Vinas FC, *et al*. 2000. Impaired cerebral mitochondrial function after traumatic brain injury in humans. *J Neurosurg* 93:815–20.
31. Fishman RA. 1975. Brain edema. *N Engl J Med* 293:706–11.
32. Kwon BK, Tetzlaff W, Grauer JN, *et al*. 2004. Pathophysiology and pharmacologic treatment of acute spinal cord injury. *Spine J* 4:451–64.
33. Tator CH, Fehlings MG. 1991. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg* 75:15–26.
34. Kobrine AI, Doyle TF, Martins AN. 1975. Autoregulation of spinal cord blood flow. *Clin Neurosurg* 22:573–81.
35. Guha A, Tator CH. 1988. Acute cardiovascular effects of experimental spinal cord injury. *J Trauma* 28:481–90.
36. Griffiths IR. 1975. Vasogenic edema following acute and chronic spinal cord compression in the dog. *J Neurosurg* 42:155–65.
37. Sandler AN, Tator CH. 1976. Effect of acute spinal cord compression injury on regional spinal cord blood flow in primates. *J Neurosurg* 45:660–76.
38. Senter HJ, Venes JL. 1978. Altered blood flow and secondary injury in experimental spinal cord trauma. *J Neurosurg* 49:569–78.
39. Lukacova N, Halat G, Chavko M, *et al*. 1996. Ischemia-reperfusion injury in the spinal cord of rabbits strongly enhances lipid peroxidation and modifies phospholipid profiles. *Neurochem Res* 21:869–73.
40. de la Torre JC. 1981. Spinal cord injury. Review of basic and applied research. *Spine* 6:315–35.
41. Beattie MS. 2004. Inflammation and apoptosis: Linked therapeutic targets in spinal cord injury. *Trends Mol Med* 10:580–3.
42. Popovich PG, Guan Z, Wei P, *et al*. 1999. Depletion of hematogenous macrophages promotes partial hindlimb recovery and neuroanatomical repair after experimental spinal cord injury. *Exp Neurol* 158:351–65.
43. Franzen R, Schoenen J, Leprince P, *et al*. 1998. Effects of macrophage transplantation in the injured adult rat spinal cord: a combined immunocytochemical and biochemical study. *J Neurosci Res* 51:316–27.
44. Rapalino O, Lazarov-Spiegler O, Agranov E, *et al*. 1998. Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. *Nat Med* 4:814–21.
45. Beattie MS, Farooqui AA, Bresnahan JC. 2000. Review of current evidence for apoptosis after spinal cord injury. *J Neurotrauma* 17:915–25.
46. Matthews HK, Nout YS. 2004. Spinal cord, vertebral, and intracranial trauma. In *Equine Internal Medicine*, edited by Reed SM, Bayly WM, Sellon DC, 566–79. St. Louis:W.B. Saunders.
47. Sweeney CR, Freeman DE, Sweeney RW, *et al*. 1993. Hemorrhage into the guttural pouch (auditory tube diverticulum) associated with rupture of the longus capitis muscle in three horses. *J Am Vet Med Assoc* 202:1129–31.
48. Brambrink AM, Dick WF. 1997. [Neurogenic pulmonary edema. Pathogenesis, clinical picture and therapy]. *Anaesthesist* 46:953–63.
49. Nout YS, Reed SM. 2005. Management and treatment of the recumbent horse. *Equine Vet Educ* 7:416–32.
50. Moore RM, Trim C. 1992. Effect of xylazine on cerebrospinal fluid pressure in conscious horses. *Am J Vet Res* 53:1558–61.
51. Tietje S, Becker M, Bockenhoff G. 1996. Computed tomographic evaluation of head diseases in the horse: 15 cases. *Equine Vet J* 28:98–105.
52. Barbee DD, Allen JR. 1986. Computed tomography in the horse: general principles and clinical applications. *proc Annual Meeting Am Assoc Equine Pract* 32:483–93.
53. Tucker RL, Farrell E. 2001. Computed tomography and magnetic resonance imaging of the equine head. V*et Clin North Am Equine Pract* 17:131–44.
54. Marshall LF, Marshall SB, Klauber MR, *et al*. 1992. The diagnosis of head injury requires a

classification based on computed axial tomography. *J Neurotrauma* 9(Suppl. 1):S287–92.
55. Green EM, Green S. 1990. Cerebrospinal fluid lactic acid concentration: reference values and diagnostic implications of abnormal concentrations in adult horses. *Proc 18th Annual Meeting* 495–9.
56. Kortz GD, Madigan JE, Goetzman BW, *et al*. 1995. Intracranial pressure and cerebral perfusion pressure in clinically normal equine neonates. *Am J Vet Res* 56:1351–5.
57. Brosnan RJ, LeCouteur RA, Steffey EP, *et al*. 2002. Direct measurement of intracranial pressure in adult horses. *Am J Vet Res* 63:1252–6.
58. Brosnan RJ, LeCouteur RA, Steffey EP, *et al*. 2004. Intracranial elastance in isoflurane-anesthetized horses. *Am J Vet Res* 65:1042–6.
59. Brosnan RJ, Steffey EP, LeCouteur RA, *et al*. 2003. Effects of duration of isoflurane anesthesia and mode of ventilation on intracranial and cerebral perfusion pressures in horses. *Am J Vet Res* 64:1444–8.
60. Brosnan RJ, Steffey EP, LeCouteur RA, *et al*. 2002. Effects of body position on intracranial and cerebral perfusion pressures in isoflurane-anesthetized horses. *J Appl Physiol* 92:2542–6.
61. Brosnan RJ, Steffey EP, LeCouteur RA, *et al*. 2003. Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses. *Am J Vet Res* 64:21–5.
62. Hillered L, Persson L, Nilsson P, *et al*. 2006. Continuous monitoring of cerebral metabolism in traumatic brain injury: a focus on cerebral microdialysis. *Curr Opin Crit Care* 12:112–8.
63. Bellander BM, Cantais E, Enblad P, *et al*. 2004. Consensus meeting on microdialysis in neurointensive care. *Intensive Care Med* 30:2166–9.
64. Rose JC, Neill TA, Hemphill JC. 3rd. 2006. Continuous monitoring of the microcirculation in neurocritical care: an update on brain tissue oxygenation. *Curr Opin Crit Care* 12:97–102.
65. Matthews HK, Andrews FM. 1990. Performing a neurologic examination in a standing or recumbent horse. *Vet Med* 1229–40.
66. Smith PM, Jeffery ND. 2005. Spinal shock—comparative aspects and clinical relevance. *J Vet Intern Med* 19:788–93.
67. Sherrington CS. 1898. Croonian lecture (1897): the mammalian spinal cord as an organ of reflex action. *Philos Trans* 190B:128–38.
68. Ditunno JF, Little JW, Tessler A, *et al*. 2004. Spinal shock revisited: a four-phase model. *Spinal Cord* 42:383–95.
69. deLahunta A. 1983. *Veterinary Neuroanatomy and Clinical Neurology*. Philadelphia:W.B. Saunders Co.
70. Calancie B, Broton JG, Klose KJ, *et al*. 1993. Evidence that alterations in presynaptic inhibition contribute to segmental hypo- and hyperexcitability after spinal cord injury in man. *Electroencephalogr Clin Neurophysiol* 89:177–86.
71. Little JW, Halar EM. 1985. H-reflex changes following spinal cord injury. *Arch Phys Med Rehabil* 66:19–22.
72. Weaver LC, Verghese P, Bruce JC, *et al*. 2001. Autonomic dysreflexia and primary afferent sprouting after clip-compression injury of the rat spinal cord. *J Neurotrauma* 18:1107–19.
73. Krenz NR, Weaver LC. 1998. Sprouting of primary afferent fibers after spinal cord transection in the rat. *Neuroscience* 85:443–58.
74. Beattie MS, Li Q, Bresnahan JC. 2000. Cell death and plasticity after experimental spinal cord injury. *Prog Brain Res* 128:9–21.
75. van Wessum R, Sloet van Oldruitenborgh-Oosterbaan MM, Clayton HM. 1999. Electromyography in the horse in veterinary medicine and in veterinary research—a review. *Vet Q* 21:3–7.
76. Nollet H, Deprez P, van Ham L, *et al*. 2004. Transcranial magnetic stimulation: normal values of magnetic motor evoked potentials in 84 normal horses and influence of height, weight, age and sex. *Equine Vet J* 36:51–7.
77. Nollet H, Van Ham L, Deprez P, *et al*. 2003. Transcranial magnetic stimulation: review of the technique, basic principles and applications. *Vet J* 166: 28–42.
78. Nollet H, Vanschandevijl K, Van Ham L, *et al*. 2005. Role of transcranial magnetic stimulation in differentiating motor nervous tract disorders from other causes of recumbency in four horses and one donkey. *Vet Rec* 157:656–8.
79. Marklund N, Bakshi A, Castelbuono DJ, *et al*. 2006. Evaluation of pharmacological treatment strategies in traumatic brain injury. *Curr Pharm Des* 12:1645–80.
80. Robertson CS, Valadka AB, Hannay HJ, *et al*. 1999. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 27:2086–95.
81. Howells T, Elf K, Jones PA, *et al*. 2005. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. *J Neurosurg* 102:311–7.
82. Finfer S, Bellomo R, Boyce N, *et al*. 2004. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 350:2247–56.
83. Gunnar W, Jonasson O, Merlotti G, *et al*. 1988. Head injury and hemorrhagic shock: studies of the blood brain barrier and intracranial pressure after

resuscitation with normal saline solution, 3% saline solution, and dextran-40. *Surgery* 103: 398–407.
84. White H, Cook D, Venkatesh B. 2006. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. *Anesth Analg* 102:1836–46.
85. Kempski O. 2001. Cerebral edema. *Semin Nephrol* 21:303–7.
86. Carlson AP, Schermer CR, Lu SW. 2006. Retrospective evaluation of anemia and transfusion in traumatic brain injury. *J Trauma* 61:567–71.
87. Robertson CS, Goodman JC, Narayan RK, *et al*. 1991. The effect of glucose administration on carbohydrate metabolism after head injury. *J Neurosurg* 74:43–50.
88. van den Berghe G, Wouters P, Weekers F, *et al*. 2001. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345:1359–67.
89. Vespa P, Boonyaputthikul R, McArthur DL, *et al*. 2006. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. *Crit Care Med* 34:850–6.
90. Busto R, Dietrich WD, Globus MY, *et al*. 1987. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab* 7:729–38.
91. Dietrich WD. 1992. The importance of brain temperature in cerebral injury. *J Neurotrauma* 9(Suppl. 2):S475–85.
92. Clifton GL, Jiang JY, Lyeth BG, *et al*. 1991. Marked protection by moderate hypothermia after experimental traumatic brain injury. *J Cereb Blood Flow Metab* 11:114–21.
93. Clifton GL, Miller ER, Choi SC, *et al*. 2001. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 344:556–63.
94. Robertson CL, Clark RS, Dixon CE, *et al*. 2000. No long-term benefit from hypothermia after severe traumatic brain injury with secondary insult in rats. *Crit Care Med* 28:3218–23.
95. Feldman Z, Kanter MJ, Robertson CS, *et al*. 1992. Effect of head elevation on intracranial pressure, cerebral perfusion pressure, and cerebral blood flow in head-injured patients. *J Neurosurg* 76: 207–11.
96. Hutchinson PJ, Corteen E, Czosnyka M, *et al*. 2006. Decompressive craniectomy in traumatic brain injury: the randomized multicenter RESCUEicp study (www.RESCUEicp.com). *Acta Neurochir Suppl* 96:17–20.
97. Timofeev I, Kirkpatrick PJ, Corteen E, *et al*. 2006. Decompressive craniectomy in traumatic brain injury: outcome following protocol-driven therapy. *Acta Neurochir Suppl* 96:11–6.
98. Bagley RS, Harrington ML, Pluhar GE, *et al*. 1996. Effect of craniectomy/durotomy alone and in combination with hyperventilation, diuretics, and corticosteroids on intracranial pressure in clinically normal dogs. *Am J Vet Res* 57:116–9.
99. Albright AL, Latchaw RE, Robinson AG. 1984. Intracranial and systemic effects of osmotic and oncotic therapy in experimental cerebral edema. *J Neurosurg* 60:481–9.
100. Soustiel JF, Vlodavsky E, Zaaroor M. 2006. Relative effects of mannitol and hypertonic saline on calpain activity, apoptosis and polymorphonuclear infiltration in traumatic focal brain injury. *Brain Res* 1101:136–44.
101. Ware ML, Nemani VM, Meeker M. 2005. Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. *Neurosurgery* 57:727–36; discussion 727–36.
102. Young B, Ott L, Twyman D, *et al*. 1987. The effect of nutritional support on outcome from severe head injury. *J Neurosurg* 67:668–76.
103. Kaufmann MA, Buchmann B, Scheidegger D, *et al*. 1992. Severe head injury: should expected outcome influence resuscitation and first-day decisions? *Resuscitation* 23:199–206.
104. Olby N. 1999. Current concepts in the management of acute spinal cord injury. *J Vet Intern Med* 13:399–407.
105. Thuret S, Moon LD, Gage FH. 2006. Therapeutic interventions after spinal cord injury. *Nat Rev Neurosci* 7:628–43.
106. Baptiste DC, Fehlings MG. 2006. Pharmacological approaches to repair the injured spinal cord. *J Neurotrauma* 23:318–34.
107. Hall ED, Wolf DL, Braughler JM. 1984. Effects of a single large dose of methylprednisolone sodium succinate on experimental posttraumatic spinal cord ischemia. Dose-response and time-action analysis. *J Neurosurg* 61:124–30.
108. Behrmann DL, Bresnahan JC, Beattie MS. 1994. Modeling of acute spinal cord injury in the rat: neuroprotection and enhanced recovery with methylprednisolone, U-74006F and YM-14673. *Exp Neurol* 126:61–75.
109. Bracken MB, Shepard MJ, Holford TR, *et al*. 1997. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. National

Acute Spinal Cord Injury Study. *J Am Med Assoc* 277:1597–604.
110. Bracken MB, Shepard MJ, Collins Jr WF, *et al*. 1992. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. *J Neurosurg* 76:23–31.
111. Bracken MB, Holford TR. 1993. Effects of timing of methylprednisolone or naloxone administration on recovery of segmental and long-tract neurological function in NASCIS 2. *J Neurosurg* 79:500–7.
112. Bracken MB, Shepard MJ, Holford TR, *et al*. 1998. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third national acute spinal cord injury randomized controlled trial. *J Neurosurg* 89:699–706.
113. Hurlbert RJ. 2001. The role of steroids in acute spinal cord injury: an evidence-based analysis. *Spine* 26(Suppl. 24):S39–46.
114. Short DJ, El Masry WS, Jones PW. 2000. High dose methylprednisolone in the management of acute spinal cord injury–a systematic review from a clinical perspective. *Spinal Cord* 38:273–86.
115. Coleman WP, Benzel D, Cahill DW, *et al*. 2000. A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in acute spinal cord injury. *J Spinal Disord* 13:185–99.
116. Sayer FT, Kronvall E, Nilsson OG. 2006. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. *Spine J* 6:335–43.
117. Hall ED. 1992. The neuroprotective pharmacology of methylprednisolone. *J Neurosurg* 76: 13–22.
118. Bracken MB, Shepard MJ, Hellenbrand KG, *et al*. 1985. Methylprednisolone and neurological function 1 year after spinal cord injury. Results of the National Acute Spinal Cord Injury Study. *J Neurosurg* 63:704–13.
119. Bracken MB, Shepard MJ, Collins WF, *et al*. 1990. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* 322:1405–11.
120. Kubeck JP, Merola A, Mathur S, *et al*. 2006. End organ effects of high-dose human equivalent methylprednisolone in a spinal cord injury rat model. *Spine* 31:257–61.
121. Zurita M, Vaquero J, Oya S, *et al*. 2002. Effects of dexamethasone on apoptosis-related cell death after spinal cord injury. *J Neurosurg* 96(Suppl. 1): 83–9.
122. Blythe LL, Craig AM, Christensen JM, *et al*. 1986. Pharmacokinetic disposition of dimethyl sulfoxide administered intravenously to horses. *Am J Vet Res* 47:1739–43.
123. Hoerlein BF, Redding RW, Hoff EJ, *et al*. 1983. Evaluation of dexamethasone, DMSO, mannitol and solcoseryl in acute spinal cord trauma. *J Am Anim Hosp Assoc* 19:216.
124. Van Meeteren NL, Eggers R, Lankhorst AJ, *et al*. 2003. Locomotor recovery after spinal cord contusion injury in rats is improved by spontaneous exercise. *J Neurotrauma* 20:1029–37.
125. Schwab JM, Brechtel K, Mueller CA, *et al*. 2006. Experimental strategies to promote spinal cord regeneration—an integrative perspective. *Prog Neurobiol* 78:91–116.
126. Pearse DD, Barakat DJ. 2006. Cellular repair strategies for spinal cord injury. *Expert Opin Biol Ther* 6:639–52.
127. Pearse DD, Bunge MB. 2006. Designing cell- and gene-based regeneration strategies to repair the injured spinal cord. *J Neurotrauma* 23:438–52.
128. Nomura H, Tator CH, Shoichet MS. 2006. Bioengineered strategies for spinal cord repair. *J Neurotrauma* 23:496–507.
129. Enzmann GU, Benton RL, Talbott JF, *et al*. 2006. Functional considerations of stem cell transplantation therapy for spinal cord repair. *J Neurotrauma* 23:479–95.

25
Disorders of the Peripheral Nervous System

Martin Furr

Trauma to peripheral nerves can be induced by various methods including pressure, stretch, or direct force (blows). These forces can arise from either internal (masses and fractures) or external sources. The range and degree of deficit that results from trauma is dependant upon numerous issues, including the degree of force applied, the location, and the amount of soft tissue covering of the nerve. In addition, stretching of nerves can induce damage particularly of the brachial plexus, whereas transection of nerves can occur secondary to wounds or fractures.

Mechanical trauma induces changes that have been classified into one of three categories: neuropraxia, axonotmesis, or neurotmesis.[1] In clinical cases, a mixture of these types is expected. Neuropraxia results from mild compressive lesion primarily resulting in bruising and inflammation of the nerve; axonal integrity is maintained. This nerve injury is transient and usually resolves within 3–6 weeks. Axonotmesis is a more severe injury, resulting from a crushing of the nerve; the epineurium and perineurium remain intact. Neurotmesis is the most severe and describes complete disruption of nervous and perineural tissues.

Mechanical injury to peripheral neurons results in a characteristic series of events to the nerve. In axonotmesis or neurotmesis, a stereotypical response occurs in the neuron. Primary degeneration involves a separation of the distal segment from the nerve cell body, and there is complete disintegration of the myelin sheath and telodendria, termed "Wallerian degeneration." Schwann cells proliferate to remove cellular debris and, in doing so, form *band fibers* (*protoplasmic bands*) along the length of the disintegrated segment. These band fibers help to guide the regenerating axon (neuritis) to the nerve termination. The axons can regrow at a rate of about 1 mm/day.[2] Only axons that reach their proper endoneurial tubes will reinnervate the distal stump and its end organ.

Following a traumatic event, as swelling of the nerve or surrounding tissue progresses, a characteristic progression of dysfunction ensues. Large diameter myelinated fibers are first compromised, resulting in loss of proprioceptive function in the affected region. Placement deficits and mild ataxia may be observed. Large myelinated motor fibers are next affected, resulting in paresis or paralysis of voluntary and reflex movement. Smaller sensory axons are next compromised, resulting in loss of sensation, and finally the smallest diameter fibers, responsible for the sensation of pain, become dysfunctional. Hence, the severity of the nerve injury can be assessed by clinical observation and the assessment of the various peripheral nerve functions.[3] Loss of deep pain perception implies a much more severe injury to the nerve than the presence proprioceptive deficits.

It may be difficult to identify specific areas of cutaneous hypalgesia due to the widespread degree of overlapping of innervated zones. Loss of sensation over a wide area of the limb suggests multiple nerve damage. Autonomous zones, which are areas that are innervated by only one specific sensory nerve, are limited in the horse, but their presence allows clinical evaluation of a specific nerve.

Following complete transaction, a muscle will loose approximately one half its mass by 2 weeks

after injury. This atrophy will continue to progress until the nerve heals, and innervation of the muscle is reestablished. Scarring and fibrosis of the muscle may limit healing, and failure to heal beyond 12 months is associated with a poor prognosis.

GENERAL TREATMENT

In the acute phase, general treatments directed at minimizing inflammation are appropriate. Systemic administration of nonsteroidal antiinflammatory agents is helpful to minimize neuronal or perineuronal swelling that may further compromise the nerve. Topical nonsteroidal pastes may also be beneficial in this regard. Dimethylsulfoxide is commonly employed for nerve and soft tissue inflammation and may be given systemically (0.5–1 g/kg IV as a 20% solution) or topically. Corticosteroids (0.05–0.2 mg/kg IV) may also be beneficial in the acute phase. Cold water hosing (hydrotherapy) or ice packs in the acute phases of the injury may help minimize the degree of inflammation. Stall confinement is prudent to minimize further injury, and wraps may be needed for support or protection from further injury.

After the acute phase has passed and local inflammation has resolved, limited exercise may be appropriate. This allows the horse to develop compensatory mechanisms and strength, but this may not be appropriate in all cases. Physical therapy in the form of hydrotherapy, muscle massages, therapeutic ultrasound, and passive flexion may help improve the horses comfort and maintain range of motion.[4] Specific treatments are further discussed below as appropriate.

SPECIFIC PERIPHERAL NERVE SYNDROMES

Facial Nerve

Facial nerve injury occurs following traumatic compression of the nerve as it passes over the facial crest or inflammation of the nerve as it passes through the middle ear or guttural pouch. Damage to the facial nucleus in the brainstem is possible and may be seen in cases of bacterial, viral or protozoal encephalitis, verminous encephalitis, or neoplasia. Damage is almost always unilateral, but bilateral disease may be seen in cases of encephalitis. Clinical signs of damage to the distal portion of the facial nerve include deviation of the muzzle away from the affected side and collapse of the ipsilateral alar fold. This is most commonly seen following recumbency during anesthesia or a tight-fitting halter. Injury of the nerve proximal to branching or involvement of the facial nucleus results in muzzle deviation away from the side of injury, ptosis, and ear droop. Tear production may be impaired resulting in corneal damage. Involvement of the facial nucleus or medulla may also result in alterations in mentation and perhaps ataxia. Owing to the proximity of the vestibular nerve, proximal injury may also be associated with signs of head tilt nystagmus or circling (Figure 25.1).



Figure 25.1. Right-sided facial paralysis in a mare. Note the dropped ear, muzzle deviation and ptosis of the right eye. This suggests very proximal or central damage to the facial nerve. Profound mental depression was also present in this mare, and bacterial meningitis was diagnosed.

Treatment is nonspecific for traumatic injury as described above. If the paralysis is secondary to another condition [e.g., equine protozoal myeloencephalitis (EPM), bacterial meningitis, temporomandibular osteoarthropathy], then specific treatment for the inciting condition is also employed.

Radial Nerve

Damage to the radial nerve most commonly occurs from external blows due to collision with stationary objects, motor vehicles, or following lateral recumbency in anesthesia. It is also commonly involved in lesions of the brachial plexus. The clinical signs associated with radial nerve injury are fairly typical and include an inability to flex the shoulder, extend the limb, and fix the elbow. This results in the horse's inability to bear weight on the limb.[5,6] The elbow remains in a slightly flexed position, with the dorsum of the hoof resting on the ground.

Brachial Plexus

Brachial plexus damage results from compression of the nerve roots comprising the brachial plexus, usually between the medial aspect of the scapula and the ribs.[7] Stretching of the nerve roots may also lead to this injury. Atrophy of the supraspinatus and infraspinatus muscles may be seen.

Musculocutaneous Nerve

Injury to the musculocutaneous nerve is rare, and transaction does not result in obvious gait abnormalities.[6] Atrophy of the biceps and brachialis muscles, with hypalgesia of the medial aspect of the forearm, may be observed.

Median and Ulnar

Damage to the median and ulnar nerves occurs secondary to fracture of the humerus or external trauma to the limb. Hyperextension of the carpus, fetlock, and pastern joints are seen, and the horse demonstrates a stiff, goose-stepping gait.[6] Hypalgesia of the medial distal aspect of the limb is seen with medial nerve damage, whereas the ulnar nerve innervates the lateral distal and caudal antebrachial aspect of the limb.

Suprascapular Nerve Damage ("Sweeny")

Damage to the suprascapular nerve results in the clinical presentation known to horsemen for generations as "Sweeny" (shoulder slip). The suprascapular nerve arises from the sixth and seventh cervical nerves and innervates the supraspinatus and infraspinatus muscles. The course of the nerve carries it across the cranial edge of the scapula. Although well protected by the brachiocephalicus, cutaneous colli, and subclavian muscles, it is susceptible to trauma from collisions with other horses, fixed objects, or kicks by nature of its adherence to the scapula.[2] Classically, poorly fitted collars on draft animals were incriminated. Injury to the nerve from stretching can occur when horses stumble with the limb placed back. Hence, injury to the suprascapular nerve appears to be most frequent in horses that are worked over uneven ground.[8] In chronic cases, scar tissue can build up, further entrapping the nerve (Table 25.1 and Figure 25.2).

Clinical signs include atrophy of the supraspinatus and infraspinatus muscles, abduction of the limb during weight bearing, and an inability to advance the shoulder. These signs were also documented following selective anesthesia of the suprascapular nerve, indicating that damage to the suprascapular nerve alone is adequate to result in clinically relevant gait abnormalities.[9] Some horses will circumduct the affected leg. The lateral movement of the shoulder joint is best observed from the front, as the horse is walking toward the examiner. Diagnosis is made predominately by observation; however, electromyography (EMG) can be useful and will show denervation of involved muscles.[10] In cases resulting from direct trauma, some involvement of the brachial plexus is common. EMG will reveal denervation after about 1 week following induction. EMG evaluation should also include evaluation of muscles in the region other than the supraspinatus and infraspinatus. Denervation of other nerves suggests more widespread injury involving the brachial plexus and may influence prognosis.

Diagnosis is sometimes not straightforward in the acutely affected animal, in which localized swelling and pain may complicate the evaluation and in which muscle atrophy is not present. Fractures of the shoulder as well as localized infection or hematoma should be considered.

General treatment is as described above. Return of function can occur in several days if the damage is minimal, but several weeks may be necessary for reinnervation of the muscle. Based upon anatomical studies and the anticipated regeneration rate for

Table 25.1. Innervation and Clinical Signs Associated with Major Nerves of the Pectoral Limb

Nerve	Muscle	Spinal Cord Segments	Clinical Signs
Suprascapular	Supraspinatus	C6 and C7	Lateral rotation and subluxation of shoulder
	Infraspinatus		Atrophy of supraspinatus and infraspinatus
Axillary	Deltoideus	C7 and C8	Atrophy of deltoid
Musculocutaneous	Biceps brachii	C7 and C8	Overextension of elbow
	Brachialis		Hypalgesia medial forearm
			Atrophy of brachialis and biceps brachii
Radial	Triceps	C8 and T1	Non–weight bearing
	Extensor carpi radialis		Inability to extend/lock elbow
	Common digital extensor		Dorsum of pastern on ground
	Lateral digital extensor		
	Ulnaris lateralis		
Median	Flexor carpi radialis	C8 and T1 and T2	Goose-stepping gait
			Dragging of toe
			Hyperextension of carpus, fetlock, and pastern
Ulnar	Superficial digital flexor	T1 and T2	Goose-stepping gait
	Flexor carpi ulnaris		Dragging of toe
			Hyperextension of carpus, fetlock, and pastern
Brachial plexus	As above	C6 and T2	Signs of radial and suprasapular nerve injury as above
			Atrophy of supra and infraspinatus, triceps, and extensor carpi

peripheral nerves (1 mm/day), function should return in about 70 days. Patients in which function has not returned in this period of time are suspected of having scar tissue entrapping the nerve.[2] Permanent fibrosis and contracture of affected muscles can occur with time, and it has been suggested that surgical decompression is recommended if there is no improvement after 90 days.[2] The procedure is described in detail in various textbooks of equine surgery, and the reader is referred to these for further discussion of the surgical technique.

Femoral Nerve Injury

The femoral nerve originates from the fourth and fifth lumbar spinal segments and innervates the quadriceps muscle. Injury has been observed following external trauma resulting in unilateral disease or dystocia and general anesthesia (bilateral disease).[11] Femoral paralysis has been associated with abscesses, tumors and aneurysms of the external iliac arteries, and fractures of the pelvis and femur.[8]

Dysfunction of the femoral nerve leads to an inability to extend the stifle, and horses cannot support weight on the affected limb. Horses with bilateral disease may dog-sit. If able to stand, they adopt a characteristic crouching position with all joints flexed and standing on the toes due to the action of the reciprocal apparatus. When walking, the limb not advanced easily, and there is a decreased stride length. The patellar reflex is absent, and there may be hypalgesia or analgesia of the medial aspect of the rear limb above the hock. Atrophy of the quadriceps muscle will be noted within 1–2 weeks. Diagnosis is

Table 25.2. Innervation and Clinical Signs Associated with Major Nerves of the Pelvic Limb

Nerve	Muscle Innervated	Spinal Cord Segments	Clinical Signs
Gluteal	Gluteals	L5 and L6 and S1 and S2	Mild abduction Outward rotation of stifle Gluteal muscle atrophy
Femoral	Quadraceps	L4 and L5	Inability to bear weight; knuckling/buckling Lack of limb extension Absent patella reflex Loss of sensation (medial thigh) Quadriceps atrophy
Obturator	Adductor Gracilus	L4–6	Abduction of rear limbs Lateral slipping
Sciatic	Semimembranosis Semitendonosis	L6–S1	Poor limb flexion Extended stifle and hock/flexed fetlock Hypalgesia (stifle down)
Peroneal	Long and lateral digital extensors	L5 and L6 and S1	Knuckling of fetlock Unable to flex hock and extend digits Hypalgesia (cranial portion of limb)



Figure 25.2. Supraspinatus and infraspinatus atrophy consistent with shoulder sweeny.

by observation and is supported by history and EMG findings. Spinal cord disease at L4 and L5 can produce similar signs and should be considered, and severe muscle disease such as exertional rhabdomyolysis and recumbency myopathy can produce similar clinical signs. Treatment is supportive and nonspecific, and the prognosis depends upon the degree of compromise. Horses that remain standing or have only one affected leg may do well with time, although it is difficult to determine the extent of the damage for purposes of giving a prognosis.

Obturator Nerve

The obturator nerve innervates the adductors of the thigh, and it may become damaged during difficult foaling. This appears to be far less common in mares than cows, but it has been reported to occur even without a history of dystocia.[8] Excessive traction during dystocia can lead to injury to this nerve be compressing the nerve between the fetus and the shaft of the ilium. Fractures of the sacrum or ilium could also lead to obturator paralysis. Clinical signs are the inability to adduct the rear limbs, and horses will go "splay-legged"—in some cases being unable to stand. Treatment is nonspecific control of inflammation, and good footing is imperative in managing such cases. Slings may be useful, but recovery of strength can take several weeks. The prognosis is guarded, with an approximate survival rate of 50% for postfoaling paralysis.[8]

Sciatic Nerve

The sciatic nerve supplies the extensor muscles of the hip and flexor muscles of the stifle, with the

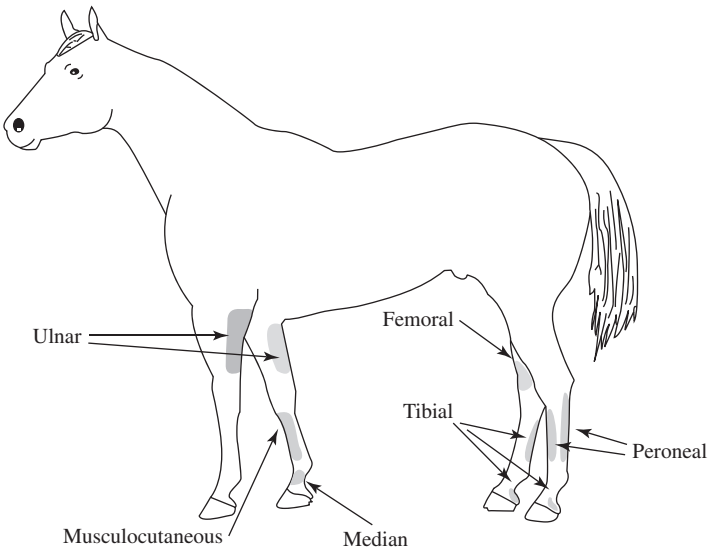


Figure 25.3. Autonomous zones of the major nerves of the front and rear limbs.

peroneal branch innervating the flexor muscles of the tarsus and extensors of the digit. The tibial branch innervates the digital flexor muscles. In the adult horse, the nerve is very deep and well protected; however in foals, it is more superficial and may be damaged by intramuscular injections. Pelvic fracture may damage the nerve, and inflammatory spinal cord disease, such as EPM, bacterial infection, or osteomyelitis can produce damage to the nerve. Sciatic nerve paralysis results in profound effects upon the gait; the limb hangs behind the horse with the stifle and hock extended. The foot cannot be advanced normally and must be dragged. If placed properly, the limb will bear weight, however. Hypalgesia extends over most of the thigh, with the exception of the medial aspect that is innervated by the femoral nerve.

The tibial branch of the sciatic nerve innervates the digital flexors. Paralysis is uncommon but results in the fetlock resting in a flexed position. When moving, the limb is overflexed with the foot carried higher than normal, and the foot is placed on the ground with excessive force. Hence, the gait is very similar to that of stringhalt.[8]

Flexors of the hock and extensors of the digits are innervated by the peroneal nerve. The nerve passes over the lateral condyle of the femur where it is susceptible to injury, typically from a kick from another horse. At rest, the horse holds the leg behind them, with the dorsum of the hoof resting on the ground. When moving, the foot cannot be advanced and is dragged forward, followed by an abrupt caudal movement during the weight-bearing phase. If the foot is manually placed, the horse can bear weight on the limb. Prognosis is considered guarded, but many horses are reported to do well with time.[8] Treatment involves local antiinflammatory treatment and protection of the limb from injury during movement.

Polyneuritis Equi

Polyneuritis equi (PNE) is an uncommon neurologic syndrome affecting horses of all ages and breeds. It has also been referred to as "cauda equina neuritis"; however, the observation that nerves outside of the cauda equina could be involved have suggested that the term PNE is preferable. It was originally described by Drexler, in 1897, in a horse with tail and anal sphincter paralysis.[12] A case reported in 1833 bears similarities also, however.[13] The condition has been intermittently reported since that time in horses from North America and Europe.[14–17] There does not appear to be a breed, gender, or age predilection, with the youngest recorded case seen in a 17-month-old horse.[18]

The etiology of the disorder is unknown; however, evidence suggests that it is an allergic-mediated polyneuropathy similar to Guillain–Barre syndrome of humans and experimental allergic neuritis (EAN) of laboratory rodents.[19,20] Infections with equine

herpesvirus-1 and camplylobacter, as well as immune-mediated reaction to *Streptococcus* sp., have been proposed, but there has not been confirmation.[17] Equine adenovirus-1 has been isolated from the spinal cord in two horses suggesting a causal association; however, further work has not confirmed this report.[21]

Research has demonstrated the presence of serum antibodies to the neuritogenic myelin protein P_2 in many animals with PNE.[19,22] This is the same antigenic protein responsible for EAN, further supporting the putative pathophysiology of the disorder in horses.

Clinical Signs

Clinical signs are typically a slowly progressive paralysis of the tail, anus, rectum, and bladder, with symmetrical hindlimb weakness and ataxia. Perineal hyperesthesia, followed by hypalgesia, may be seen; in some cases, the area of hypalgesia is surrounded by a zone of hyperesthesia. Perineal hyperesthesia may present as tail rubbing in the early stages. Penile prolapse with urine dribbling can be seen in males. Muscle atrophy is variably present. Cranial nerve dysfunction may also be seen coincident with or preceding the caudal signs. The cranial nerve signs are often asymmetric, in contrast to the caudal signs. Paralysis of masticatory and facial muscles, head tilt, nystagmus, tongue paralysis, and difficulty swallowing have all been reported. Impotence has been reported in stallions due to urospermia and erection failure.[23]

Diagnosis

Currently, no specific antemortem diagnostic test exists for the diagnosis of PNE. The diagnosis is primarily one of exclusion, supported by the presence of clinical signs of cauda equina syndrome and cranial nerve deficits. The presence of high serum concentrations of P_2 antibody is supportive; however, the test is not commercially available and is not specific for PNE.[19]

Routine clinicopathologic testing is indicated in the evaluation of horses with this presentation, and evidence of chronic inflammation is usually observed. Cerebrospinal fluid is often abnormal. Xanthochromia, with a mildly increased cell count and total protein, is common.[15,24]

Many rule outs should be considered before making a diagnosis of PNE. Equine herpesvirus-1 myeloencephalitis, rabies, sacral fracture, meningitis, sorghum cystitis, and verminous myelitis should all be considered. Evaluation as discussed in Section 2, Chapter 9, should be performed. A particularly important consideration is EPM, which can have a very similar clinical presentation. Horses with EPM do not usually have changes in the cerebrospinal fluid and should have a positive immunoblot. It may be very difficult to discriminate between the two conditions, however.

The definitive diagnosis is made on postmortem examination. Extradural and intradural nerve roots of the cauda equina are grossly thickened and have infiltration of inflammatory cells. Demyelination and axonal degeneration are present.[25] The changes are typically worse in the cauda equina but changes of cranial nerves may also be observed.

Treatment

The primary treatment is palliative, including management of urinary and fecal incontinence, managing cystitis, and minimizing urine scalding. Horses that have difficulty eating may need tube feeding. Treatment with corticosteroids, preferably dexamethasone (0.05–0.1 mg/kg), has provided some palliative benefit, but most authors consider the effects short lived. The condition is slowly progressive, but the overall outcome is generally poor.

REFERENCES

1. Seddon HJ. 1943. Three types of nerve injury. *Brain* 66:237–88.
2. Schneider RK, Bramlage LR. 1990. Suprascapular nerve injury in horses. *Comp Cont Educ Pract Vet* 12:1783–90.
3. Blythe LL. 2003. Limb weakness, atrophy, and other signs of peripheral nerve disease. In *Current Therapy in Equine Medicine*, edited by Robinson NE, 735–40. St. Louis:Saunders.
4. Andrews FM, Mathews HK, Reed SM. 1990. Medical, surgical and physical therapy for horses with neurologic disease. *Vet Med* 85:1229–35.
5. Rooney JR. 1963. Radial paralysis in the horse. *Cornell Vet* 53:328–31.
6. Henry RW. 1976. Gait alterations in the equine pectoral limb produced by neurectomies. *Thesis*. Ohio State University.
7. Mayhew IG. 1989. *Large Animal Neurology*. Philadelphia:Lea and Febinger.

8. Hahn CN, Mayhew IG, MacKay RJ. 1999. Diseases of the peripheral (spinal) nerves. In *Equine Medicine and Surgery*, edited by Colahan PT, Merritt AM, Moore JN, Mayhew IG, 975–80. St. Louis:Mosby.
9. Devine DV, Jann HW, Payton ME. 2006. Gait abnormalities caused by selective anesthesia of the suprascapular nerve in horses. *Am J Vet Res* 67:834–6.
10. Andrews FM. 1987. Electrodiagnostic aids in neurologic disease. *Vet Clin North Am Equine Pract* 3:293–322.
11. Dyson S, Taylor P, Whitwell K. 1988. Femoral nerve paralysis after general anaesthesia. *Equine Vet J* 20:376–80.
12. Drexler H. 1897. Uber die combinierte chronische Schweiflahmungund Sphinkterenparalyse des Pferdes (Hammelschwanz). *Z Tiermed* 279–99.
13. Bainbridge G. 1833. A case of palsy of the lips. *Veterinarian* 6:638.
14. Rousseaux CG, Futcher KG, Clark EG, *et al*. 1984. Cauda equina neuritis: a chronic idiopathic polyneuritis in two horses. *Can Vet J* 25:214–8.
15. Wright JA, Fordyce P, Edington N. 1987. Neuritis of the cauda equina in the horse. *J Comp Pathol* 97:667–75.
16. Greenwood AG, Barker J, McLeish I. 1973. Neuritis of the cauda equine in a horse. *Equine Vet J* 5:111–5.
17. Scarratt K, Jortner BS. 1985. Neuritis of the cauda equina in a yearling filly. *Comp Cont Educ Pract Vet* 7:S197–202.
18. Vatistas NJ, Mayhew IG, Whitwell KE, *et al*. 1991. Polyneuritis equi: a clinical review incorporating a case report of a horse displaying unconventional signs. *Prog Vet Neurol* 2:67–72.
19. Kadlubowski M, Ingram PL. 1981. Circulating antibodies to the neuritogenic myelin protein, P2, in neuritis of the cauda equina of the horse. *Nature* 293:299–300.
20. Hanhn CN. 2006. Miscellaneous disorders of the equine nervous system: horners syndrome and polyneuritis equi. *Clin Tech Equine Pract* 5:43–8.
21. Edington N, Wright JA, Patel JR, *et al*. 1984. Equine adenovirus 1 isolated from cauda equina neuritis. *Res Vet Sci* 37:252–4.
22. Fordyce PS, Edington N, Bridges GC, *et al*. 1987. Use of an ELISA in the differential diagnosis of cauda equina neuritis and other equine neuropathies. *Equine Vet J* 19:55–9.
23. Held JP, Vanhooser S, Prater P, *et al*. 1989. Impotence in a stallion with neuritis cauda equine: a case report. *J Equine Vet Sci* 9:67–8.
24. White PL, Genetzky RM, Pohlenz JF, *et al*. 1984. Neuritis of the cauda equina in a horse. *Comp Cont Educ Pract Vet* 6:S217–23.
25. Summers B. 1995. Diseases of the peripheral nervous system. In *Veterinary Neuropathology*, edited by Summers B, Cummings JF, de Lahunta A, 402–501. St. Louis:Mosby.

26
Equine Neurotoxic Agents and Conditions

Martin Furr

Specific neurointoxications appear to be rare in the horse, yet there remain a substantial number of compounds which can result in neurologic illness, either as a primary or secondary illness. Any horse that is severely shocked or compromised might well demonstrate weakness and ataxia as a secondary sign yet not have specific neurologic disease. This is often difficult to discriminate in the clinical setting. Compounds discussed below demonstrate specific neurotoxic properties in the horse or result in clinical signs in which neurologic deficits are a major presenting sign. The effects of many of the compounds are very poorly described in the equine species and literature and are represented by very few cases.

PHARMACEUTICAL TOXICITY

Fluphenazine

In veterinary medicine and equine practice in particular, the phenothiazine derivative tranquilizers have been an important contribution to the management of many conditions. The most commonly used compounds of this class, promazine and acetylpromazine, have a wide margin of safety, but a short duration of action. In conditions where longer duration of activity is desired, other phenothiazine formulations which are not approved for use in the horse have been used including fluphenazine, perphenazine and pipothiazine. Phenothiazines with extended duration of activity are used in humans as an antipsychotic and they act by blocking dopamine receptors in the limbic region of the brain; as a group, they are referred to as neuroleptics.[1] In addition, however, they also block dopamine receptors in the striatum, leading to a variety of side effects referred to as the extrapyramidal syndrome (EPS). This syndrome is characterized by involuntary muscle spasms, particularly of the head and neck and proximal extremities (dystonia) as well as a motor restlessness which causes the patient to pace or rock uncontrollably (akathisia).

Although not approved for use in the horse, fluphenazine has been used as a long-term sedative for horses with behavioral problems. Conventional doses given to adult horses range from 25 to 50 mg intramuscularly every 3–4 weeks. This dosage is not based upon any known pharmacokinetic analysis, and the metabolism and clearance of the drug is totally unknown in the horse. Horses have demonstrated typical EPS-like signs following these doses; it has also been observed in horses in which this drug had been used previously with no observed complications.

In reported cases, the clinical signs have been noted to begin at 14 to 36 h after administration.[2,3] Clinical signs include restlessness and agitation, accompanied by sweating and muscle tremors. Uncontrollable gross body movements may occur, with the horse crashing into walls and staggering. Characteristically there are writhing movements of the head and neck associated with a repetitive striking movement of one or both front legs. Horses are commonly noted to refuse to move forward. The clinical presentation can be confused with a seizure and can lead to self-induced injury to the horse as well as put owners or handlers at risk of injury. Horses suffering from this condition are not typically aggressive toward people, but the horses must be handled with caution.

Treatment is symptomatic and has involved the use of a variety of sedatives and/or anticonvulsants for immediate control, in some cases coupled with the anticholinergics benztropine or diphenhydramine hydrochloride.[1–3] The severity of the condition will dictate treatment, and not all drugs appear to work in all cases. Xylazine or detomidine will provide transient relaxation in many cases, sometimes lasting only several minutes. Phenothiazine tranquilizers should be avoided due to the potential to worsen the clinical signs. Combinations of intravenous pentobarbital (4.8 mg/kg loading dose and 1.2 mg/kg maintenance as needed) and phenobarbital (1 mg/kg) have been reported to control the clinical signs and allow the horse to stand quietly and eat.[2] In another report, a horse responded to intravenous administration of diphenhydramine hydrochloride (0.6 mg/kg). Clinical signs abated within minutes and remained absent for another 18 h, after which time a second dose given with equal effect. The author's experience with the use of diphenhydramine for the control of EPS is variable, with some horses not responding at all. Benztropine (0.035 mg/kg PO q 12 h; 0.018 mg/kg IV q 12 h) has been used in horses with EPS resulting from fluphenazine toxicity with good results.[3] In most reported cases, as well as the author's clinical experience, most horses recover within 5–7 days with no long-term effects.

One case of EPS associated with administration of the neuroleptic pipothiazine palmitate (250 mg IM) has been described, with clinical signs identical to fluphenazine.[4] Clinical signs in this case occurred 5 days after injection, and the horse recovered over several days with empirical clinical management using diazepam (10 mg q 4 h).

Ivermectin and Moxidectin

Overdose with the anthelmintic ivermectin can result in neurologic disease. A 10X dose of ivermectin given to a zebra foal resulted in depression, ataxia, and blindness which began approximately 12 h after administration.[5] The zebra recovered and was considered normal by 5 days after ingestion. Other reported cases were also foals, which were inadvertently given an entire syringe of the product. Clinical signs were similar, and one foal died 18 h after ingestion associated with severe bradycardia.[5] This is similar to other reports in which a 10X overdose orally to adult horses resulted in blindness, ataxia, and depression, which persisted for 4 days.[6] With injectable ivermectin, doses of 15X resulted in mild neurologic signs (mydriasis).[6] Lower doses of ivermectin (2X–3X) have been reported to cause toxic signs in foals which have had a previous neurologic disease.

Ivermectin causes paralysis of nematodes and arthropods by potentiating the release of gamma aminobutyric acid (GABA).[7] GABA is also an inhibitory neurotransmitter found in vertebrates and invertebrates. GABA blocks post-synaptic transmission of nerve impulses. This is the basis for neurotoxicity; however, ivermectin does not readily cross the blood–brain barrier, hence the potential for toxicity is minimized.

Overdose with moxidectin has also resulted in neurologic signs in horses.[8,9] Moxidectin is a macrolide anthelmintic which is structurally similar to the avermectins but is in the chemical class of milbemycins. Overdose with moxidectin can result in signs of coma, dyspnea, depression, ataxia, trembling, seizures, and muscle weakness.[9] The approximate dose at which these signs were seen was from 1.0 to 5.0 mg/kg, which is 2.5 to 13 times the approved label dosage of 0.4 mg/kg. Clinical signs have been seen in young foals (<4 months of age) after a single dosage of 5X the label dose or 3 consecutive daily doses of 3X the label dose.[10]

Most reported cases are in foals, with adults seemingly less commonly affected. This has been proposed to be due to an increased sensitivity of foals to the toxic effects of the drug but may simply be that foals are more likely than adults to be given an overdose due to the nature of the drug delivery system (i.e., an oral dose syringe). Failure of the syringe-locking mechanism or intentional administration of the entire tube have both been reported as causes of the overdose. The mechanism of toxicity is believed to be similar to that of ivermectin.

Clinical signs are noted from 6–18 h after administration, and signs persisted for 36–168 h. In contrast to ivermectin overdosage, blindness has not been reported with moxidectin overdose.

Treatment of either ivermectin or moxidectin overdose is primarily supportive. If an overdose is quickly identified, oral activated charcoal can be given. Intravenous fluid support may be necessary for severely affected animals. Dimethylsulfoxide and/or corticosteroids can be given; however, their efficacy for the treatment of this condition is

unknown. Control of seizures and self-induced injury may be required and should be determined on a case by case basis. The majority of reported cases recovered with supportive care; however, one affected foal died despite intensive supportive care.[8]

Tentative diagnosis can be determined by the clinical signs and history of exposure. No typical clinical chemistry abnormalities are expected with ivermectin or moxidectin overdose. Serum, plasma, liver, kidney, or adipose tissue can assayed, but toxic levels in horses are not known.[9]

Haloxon

Bilateral laryngeal paralysis has been reported following the use of haloxon as an anthelmintic in foals. At doses of 1 and 2 g every 14 days, several foals developed dyspnea after 3 doses of haloxon. A stiff gait was also described antemortem, but this was not evaluated in detail. Biopsy of the recurrent laryngeal nerves found nerve cell death, Wallerian degeneration, and demyelination.[11]

Levamasol

Levamasol is occasionally used in the horse as an anthelmintic and potential immunomodulator. The toxic dose is 20 mg/kg BW, and clinical signs (sometimes resulting in death) have been seen within 1 h of administration.[12] Hyperexcitability, muscle tremors, hyperactivity, excessive sweating, and lacrimation have been reported.[13] Treatment is supportive, and clinical signs generally resolve within 12 h in survivors.

Propylene glycol

Propylene glycol is commonly present in the veterinary environment and is used to treat bovine ketosis. Due to the similarity of appearance and storage, inadvertent administration of propylene glycol has occurred in horses.[14–16] Oral dosing of 3/4 gallon of propylene glycol in a clinical patient resulted in severe depression and ataxia, and doses of half to one gallon resulted in depression and ataxia which was transient and resolved within 3 days with no specific treatment. Two gallons of propylene glycol administered to an adult horse resulted in recumbency, followed by severe diarrhea; the horse died after 3 days.[15] Treatment is supportive; administration of activated charcoal may be beneficial.

Ionophores

Ionophore compounds are polyether antibiotics that include the compounds monensin, lasalocid, salinomycin, narasin and maduromycin. Although primarily a cardiotoxin, signs of neurologic disease can be seen with acute ionophore toxicity. Toxicity with monensin is the most commonly reported, presumably because monensin has been in commercial use for the longest time, although toxicity with salinomycin has also been reported.[17–19]. Horses gain access to the ionophores due to mixing errors or accidental feeding with treated cattle feed.

The ionophores are a family of compounds which transport specific alkali metal cations across cell membranes.[17] Specifically, ionophores are selective in their influence on the movement of sodium and potassium ions between intracellular and extracellular spaces. A secondary influence upon calcium (Ca) is also recognized. In fact, the myocardial and skeletal muscle toxicity of ionophores is probably related to the increase in intracellular Ca, which initiates a series of events leading to cell death.[20,21]

Neurologic abnormalities associated with ionophore toxicity are depression and ataxia which are noted within 24–48 h of consumption of monensin. Horses demonstrate weakness of the rear limbs, reluctance to move, and stumbling. They may lie down and then stand frequently, until such time that they remain recumbent.[22,23] Profuse sweating is noted in horses with monensin, but not lasalocid intoxication.[19] Poisoning with salinomycin results in similar clinical signs, although some horses showed acute swelling of the masseter and eyelid regions.[18] It is unclear if the neurologic signs observed are simply a result of the combined effects of abdominal pain, myopathy, and shock, or if a specific neuropathy is present, as the nervous system in such cases has not been carefully examined. Other conditions to consider in the list of differential diagnoses are exertional myopathy, intoxication with white snakeroot or coffee senna, blister beetle intoxication, nutritional myodegeneration, or primary myocardial disease.

Diagnosis of ionophore intoxication antemortem is challenging and is greatly aided by a careful history suggesting a feed change or the possibility of consumption of intoxicated feeds. Clinical signs are not specific but typically laboratory evaluation will demonstrate hemoconcentration, hypokalemia, and hypocalcemia.[17,19,23]

Horses appear to be very sensitive to the effects of ionophores, and feed containing 279 ppm monensin is lethal to adult horses, while feed with 125 ppm monensin is toxic, although not fatal.[22] The LD50 of monensin for horses has been estimated to be 2–3 mg/kg body weight, while 20 mg/kg body weight is fatal.[22] The LD50 of lasalocid for horses has been estimated to be 21.5 mg/kg body weight.[23]

Treatment for ionophore toxicity is primarily supportive as there is no specific antidote. The use of vitamin E and selenium is suggested in other species but is unproven in the horse.[19]

ENVIRONMENTAL TOXINS

Bromide

Methyl bromide has been used as a soil fumigant, and ingestion of hay from fumigated fields has resulted in signs of ataxia in horses.[24] Clinical signs include ataxia, an "ambling" gait, and dragging of the feet. Hay from the fumigated field was found to have a bromide concentration of 6,800 ppm, and serum from affected horses had a bromide concentration of 36.9 mEq/L.[24] In a test feeding, horses developed clinical signs after 7 days of consuming the affected hay. This resulted in a total consumption of 49 g of bromide ion per day. Prognosis for bromide intoxication is variable, and eliminating the source of bromide and supportive care has sometimes been successful.

Urea

Poisoning with urea is rare in the horse but has been reported to occur occasionally.[25] Horses may become intoxicated by accidental feeding of ammonia or by gaining access to urea-treated cattle feeds. Aimless wandering, incoordination, depression, head pressing, convulsions, and death have been observed in ponies fed with 450 g of ammonia. Diagnosis is made by detection of increased blood and/or cerebrospinal fluid (CSF) ammonia concentrations in the absence of liver disease. Treatment is supportive and the prognosis is considered poor, although there are limited equine reports to confirm this position.

Organophosphates

Organophosphates are commonly used as animal insecticides and parasiticides, plant insecticides, herbicides, rodenticides, and insect repellants. There is a bewildering array of organophosphate formulations, each with subtle differences in metabolism, toxic potential, and clinical effects.

Organophosphates are readily absorbed from the gastrointestinal tract or through skin.[12] They exert their toxic action by irreversible inhibition of cholinesterase and pseudocholinesterase resulting in the accumulation of acetylcholine at neuromuscular junctions, cholinergic synapses within the central nervous system (CNS), and parasympathetic postganglionic sites.[12] Clinical signs are a direct consequence of this overstimulation.

Profuse salivation, lacrimation, and nasal discharge are observed due to the stimulation of muscarinic cholinergic sites. Due to increased secretion and muscular contraction, abdominal pain and diarrhea may be seen. Bradycardia, miosis, sweating, and frequent urination are observed. Neurologic abnormalities include muscle stiffness and fasciculations, tremors, and a stiff, awkward gait. Anxiety, nervousness, and hyperactivity may be seen due to the diffuse CNS stimulation arising from overstimulation of the nicotinic cholinergic receptors.

The clinical syndrome of organophosphate toxicity is fairly characteristic and, coupled with a history of exposure, should provide a presumptive diagnosis. Confirmation is best attempted antemortem by determining cholinesterase activity in blood or other body tissue. Blood cholinesterase activity of $>25\%$ of normal are considered confirmatory.[12] Differential considerations include carbamate toxicity, blister beetle, botulism, colic, and pheochromocytoma.

Treatment of organophosphate intoxication is most readily attempted with atropine sulfate. A dose of 0.2 mg/kg BW has been recommended, with one-fourth given IV and the remainder subcutaneously or intramuscularly. This can be repeated as necessary at 3–6 h intervals, with the minimum amount possible used to minimize the risk of gut stasis and colic.[12] Muscle fasciculations may not be affected by atropine treatment.

Other treatment options include the use of an oxime compound, 2-PAM (pralidoxime chloride. This will free the organophosphate from the receptor. The recommended dose varies between 20 and 50 mg/kg BW IV, and it should be given after atropine to optimize its action. Phenothiazine tranquilizers, succinylcholine, and morphine should

specifically be avoided in suspect organophosphate intoxication cases.

Carbamates

Intoxication with the carbamate pesticides results in clinical signs which are very similar to the organophosphates. As the carbamates are reversibly bound to the cholinesterase receptor, they can be removed by spontaneous hydrolysis and consequently the clinical signs resulting from intoxication tend to be short-lived (36–48 h).

Diagnosis is as for the organophosphates, and chemical analysis of tissues or fluids are often unrewarding. Confirmation of the compound in stomach contents may be helpful in confirming exposure.

Recommended treatment is atropine sulfate (0.2 mg/kg BW, 1/4 IV and the remainder subcutaneously or intramuscularly). The oxime compounds should not be used in cases of suspected carbamate toxicity as they are of no benefit and may in fact worsen the clinical signs in cases of carbaryl poisoning. Activated charcoal can be given, but mineral oil should be avoided as it may enhance absorption of the compound.[12]

Nicotine

Nicotine sulfate has been used as a plant insecticide, premise spray, and historically as an ectoparaciticide. In addition, the shrub pituri (*Duboisia hopwoodii*) is widely distributed in western Australia and it contains nicotine; horses have been poisoned by grazing the plant.[26] The lethal dose of nicotine in the horse is reported to be 100–300 mg.[12] Nicotine is readily absorbed from the oral mucosa, gastrointestinal tract, respiratory tract, and intact skin.

Nicotine stimulates autonomic nervous system ganglia, neuromuscular junctions, and some synapses in the CNS by interaction with the nicotonic receptor and subsequent depolarization of the postsynaptic membrane. In larger concentrations, this initial depolarization is immediately followed by blockade of the receptor. Death is due to paralysis of respiratory muscles, owing to blockade of the neuromuscular junction.

Clinical signs of intoxication include signs of cholinergic stimulation (agitation, nervousness, salivation, tachypnea, diarrhea), shortly followed by depression, muscle weakness, ataxia, and an increased heart rate. In humans, low blood pressure, mental confusion, and weak pulse are prominent.[27] Seizures may occur, and progression to prostration and death due to respiratory paralysis can occur.[12]

Diagnosis is established by the clinical signs of cholinergic stimulation followed by paralysis, accompanied by a history of potential exposure. There are no characteristic clinicopathological changes, and no observable abnormalities on postmortem. The odor of tobacco may be present in gut content if the toxin is ingested. There is no antidote, and treatment is supportive and empirical. Activated charcoal can be given, and the horse washed, if the exposure was cutaneous. Atropine is not considered to be of value.

Mercury

Intoxication of horses with mercury has only rarely been reported, but chronic ingestion of grain treated with fungicidal mercury compounds can be a source of intoxication.[28] Clinical signs of ataxia, hypermetria, muscle trembling, and head bobbing were noted. Chronic ingestion of phenylmercuric acetate (0.672 mg/kg for 191 days) resulted in dermatitis, gingival swelling and necrosis, weight loss, and masseter muscle atrophy. Dullness, depression, and weakness were also seen. It is unclear if these signs were associated with primary neurologic disease or were merely secondary signs.[29] Poisoning with mercuric chloride did not result in neurotoxicity.[30] One horse suffered intoxication from a mercuric blister applied to treat a leg injury, but the clinical signs included renal failure and dermatitis; no neurologic signs were noted.[31] In another horse treated with a mercury blister (mercury chloride in herb and alcohol base; 5.3% mercury) for a leg wound, mercury toxicity ensued and was expressed as renal failure, colic, and ventral edema.[32] No clinical neurologic signs were detected, but neuronal necrosis and edema of the brain was evident on postmortem examination.[32]

Lead

Horses become exposed to lead via ingestion of forage contaminated by aerial fallout of lead surrounding smelting plants or highway rights of way, chewing on surfaces painted with lead-based paint, or from ingestion of lead-based orchard herbicidal sprays. These sources lead to the chronic form of lead toxicity (plumbism). Acute lead intoxication

appears to be very uncommon in horses due to their selective eating habits; however, it has been reported from ingestion of paint and motor oil.[33,34] In developed countries, public health policies to decrease environmental contamination with lead have probably resulted in the seemingly less common presentation of this disorder in the horse in recent years.

A daily intake of 1.7 mg/kg for several months will result in classic signs of chronic lead toxicity.[35] This corresponds to the average daily consumption of forage with 80 ppm lead (dry weight). Limited data are available on acute toxicity of horses with lead, but one horse was given 1,000 mg of lead/kg with only nonspecific clinical signs.[36]

Lead disrupts nerve transmission, probably by interference with the availability of Ca.[37] Lead also interfered with the uptake of dopamine and the metabolism of GABA.[37] Motor nerves are more susceptible than sensory nerves. This is consistent with the clinical presentation.

Chronic ingestion of lead commonly leads to signs of peripheral neuropathy. The most commonly noted neurologic signs in horses include dysphagia and abnormal phonation (roaring) due to pharyngeal and laryngeal paralysis. Other clinical signs include facial paralysis, muscle weakness with ataxia, dysmetria of the tongue and lips, and anal sphincter paresis. Cerebral signs such as depression are rare in horses but can be seen in severe intoxications. Inhalation pneumonia may develop secondary to the dysphagia. Colic and protein-losing enteropathy with ventral edema have been reported occasionally. Joint swelling and lameness can be seen in young growing animals. A blue "lead line" around the base of the teeth has also been reported in the horse. In a summary of reported lead intoxications of the horse, roughened hair coat was the most common clinical sign (53% of cases) and weight loss was seen in 36% of the cases.[33] Neurologic signs, such as incoordination (20% of cases) or laryngeal dysfunction (44% of cases) were commonly seen as well.

Clinical chemistry analysis of horses with lead toxicity is usually normal, although nonspecific changes may be noted in horses with colic or pneumonia. Hypoproteinemia is occasionally seen, and mild dehydration may be seen in horses with colic or dysphagia. White blood cell counts are usually normal unless the illness is complicated by pneumonia or colic. Anemia was reported in 22% of the reported cases[33] and is usually mild when seen.[34] Immature red blood cells (RBCs) and basophilic stippling are sometimes seen.

Diagnosis is supported by clinical signs and history of exposure, accompanied by assays of blood or urine for lead. Concentration of blood lead greater than 0.35 ppm should be considered significant; however, lower values do not rule out lead toxicity due to sequestration of lead in bone.[34] In addition, there seems to be little correlation of blood lead concentrations and the severity of the clinical signs. An increase of urine lead concentration ($>$1 ppm) following chelation treatment is also supportive of lead poisoning. Anemia or dehydration can alter blood concentrations, and interpretation of blood lead concentrations in such animals should be done with caution. In cases of chronic poisoning, blood lead concentrations may be low, due to redistribution of lead to peripheral tissues. CSF evaluation is usually normal, and electromyography (EMG) findings in one horse with lead intoxication were normal.[33] Assay of liver or kidney can be used to confirm lead intoxication.

Other inferential assays for lead toxicity include increased urine delta aminolevulinic acid ($>$200 mg/dL), but alteration of this compound appears to be inconsistent in the horse. In addition, the presence of increased free erythrocytoporphyrin concentrations correlates directly with blood lead concentrations. These assays are rarely used in clinical practice.[34,38]

Recommended treatment is chelation with 6.6% calcium disodium EDTA (calcium versenate). This will mobilize lead from peripheral tissues and enhance clearance. The recommended dosage is 50–100 mg/kg of calcium versenate given intravenously once per day for 3 days, then repeated after a nontreatment interval of 4 days. Repeated blood and urine assays should reveal decreasing concentrations, and treatment can be discontinued when normal values are obtained. The duration of treatment necessary to obtain clearance is unknown, but in 2 reported cases, 10 days of treatment was adequate.[33] In addition to chelation therapy, thiamine (1 mg/kg, once per day) can be given and is reported to be beneficial. Ancillary treatments are dictated by the nature of the horse's other clinical problems. Long-term prognosis is unknown, but mild clinical signs may persist.

Strychnine

Strychnine is used as a rodenticide and has only rarely been reported to cause toxicity in the horse.[39] Clinical signs appear rapidly following ingestion and include apprehension, nervousness, and muscle stiffness, followed by violent tetanic seizures. The seizures may be interspersed between periods of relaxation.

Strychnine competitively antagonizes the inhibitory neurotransmitter glycine in the spinal cord, resulting in hyperexcitation of muscles. No specific antidote exists, and treatment is supportive and empirical. Control of seizures with pentobarbital or phenobarbital is recommended. Chloral hydrate has also been suggested as a sedative; however, availability may be an issue, and the author has seen little effect from the use of chloral hydrate in the horse. The centrally acting muscle relaxant methocarbamol (150 mg/kg BW) and guaifenesin (110 mg/kg IV) can be given as needed.[12] Activated charcoal can be given in an effort to neutralize the toxin.

Molluscicides

The molluscicides metaldehyde and methiocarb have been incriminated in the horse only very rarely. Horses become intoxicated by inadvertent consumption of the compounds placed around ornamental plants or crops.[12] Horses may be more susceptible than dogs to the effects of metaldehyde, and ingestion of a single dose of 60 mg/kg BW and 120 mg/kg BW resulted in the death of 2 horses.[40,41] Methiocarb has been reported to result in toxicity at an estimated dosage of 100–125 g.[42,43]

Clinical signs observed with both compounds include nervousness and anxiety, sweating, and muscle fasciculations progressing to tremors and seizures. Death occurred rapidly (within a few hours) in horses intoxicated with metaldehyde, while 1 horse intoxicated with methiocarb lived and clinical signs resolved after 12 h.[43]

Diagnosis is by observation of clinical signs and history of exposure. Analysis of stomach content for acetaldehyde has been suggested, and a formaldehyde-like odor may be recognized in the stomach in cases with metaldehyde toxicity.[12] Treatment of intoxication is supportive, including administration of activated charcoal, intravenous fluid support, and control of seizure activity with phenobarbital and valium. Methocarbamol (150 mg/kg BW) may be beneficial to control muscle fasciculation.

The antidote for methiocarb is atropine sulfate, which can be given as needed. Supportive care as discussed above is also beneficial.

4-Aminopyridine

Intoxication with 4-aminopyridine (a bird repellant often mixed with grain) has been reported in 1 horse, which had signs of profuse sweating, behavioral abnormalities, fluttering of the eyelids, and convulsions.[44] The estimated lethal dose is 2–3 mg/kg BW. The mechanism of action is not known, but the overall effect is CNS stimulation. No specific antidote is known. Diagnosis has been confirmed by HPLC of stomach content.[44]

Amitraz

There "Amitraz" is 1 report of intoxication following topical application of the acaricide amitraz.[45] Topical application of a 0.025% solution resulted in clinical signs of colic and large colon impactions, tranquilization, depression, and ataxia. It appears that intoxication is due to chemical breakdown of the amitraz to the highly toxic chemical 3,5-dimethylphenyl *N*-methyl formamidine during storage prior to application.[45] Treatment is symptomatic, and affected horses recovered completely over a period of several days.

PLANT AND FORAGE ASSOCIATED INTOXICATIONS

White Snakeroot and Rayless Goldenrod

White snakeroot is a common plant in wooded areas of the eastern and central United States, extending as far north as Michigan (Figure 26.1).[12] Rayless goldenrod, or jimmyweed, is a shrub primarily found in the southwest United States. The toxic principle of both plants is tremetol, a fat soluble alcohol. Ingestion of these plants results in a clinical syndrome referred to as the "trembles", due to the characteristic muscle fasciculations that they produce. An interesting historical note is that tremetol in milk from cows consuming white snakeroot was responsible for the condition known as "milk sickness" in humans.

The mechanism of action of the toxin is unknown, but clinical signs will result from ingestion of 1–10% of body weight of the green plant and may be fatal.[46] The plant remains toxic after drying



Figure 26.1. Typical appearance of white snakeroot. Photo courtesy of Dr. Blair Meldrum.

and in hay. Clinical signs of toxicity can appear up to 3 weeks after exposure to the plant. Predominant clinical signs are dilated pupils, depression, and a stiff gait with muscle tremors, with patchy sweating and cardiac arythmias.[46] Dysphagia and hypersalivation have also been seen.[47]

Increased muscle enzyme activity is typically noted, along with hemoglobinuria, hyperglycemia, and acidosis.[12,46] Postmortem findings include colitis, renal tubular necrosis, pericarditis, myocarditis, and myositis.[46] Diagnosis is supported by the clinical observation of muscle tremors associated with myositis and cardiomyopathy and the potential for exposure to the plant. Assay of body fluids for the toxic principle has not been successful.[12] There is no specific antidote, and treatment is symptomatic.

Solanaceae species

Several members of the *Solanum* family have been reported to cause toxicity in the horse. Plants within this family contain either the atropine-like or solanum alkaloids. *Datura* spp. (jimsonweed), *Atropa belladonna* (deadly nightshade), and *Dubosia* spp. (corkwoods) contain atropine alkaloids. These plants are generally unpalatable but can become included in hay, where they retain toxicity. Ingestion of an unknown quantity of jimsonweed resulted in the death of 11 out of 15 ponies with clinical signs of depression, excessive urination, diarrhea, mydriasis, muscle spasms, and convulsions.[47] Physostigmine can be used to effect in horses affected by the atropine containing plants. Black nightshade (*Solanum nigram*) contains the solanum alkaloid toxin, and ingestion by horses results in colic, ataxia, weakness, tremors, and convulsions. Atropine is a logical treatment for the solanum containing plants.

Nigropallidal encephalomalacia

Ingestion of Yellow star thistle (*Centaurea solstitialis*) and Russian knapweed (*Acroptilon repens*, previously *Centaurea repens*) results in a syndrome referred to as nigropallidal encephalomalacia (NE).[48–51] In addition, it has been suggested that the Malta star thistle (*Centaurea melitensis*), native to Central Texas, may also cause the disease but specific reports cannot confirm this.[52]

These plants are abundant in non-improved or non-irrigated fallow pastures in their native range, where they tend to persist in the summer and late fall. This corresponds to the prevalence of clinical illness; in one report, a peak of cases was seen in mid summer (June and July) and another peak in the fall (October and November).[47] The plant remains toxic in hay.[53] Cases due to yellow star thistle have also been documented in Australia and Argentina.[54]

Yellow star thistle is most abundant in the United States in California, southern Oregon, and Idaho, and is spreading eastward, with sporadic distribution. Yellow star thistle has a single erect woody stem, 1–6 feet in height, topped with a cluster of bright yellow flowers. Russian knapweed has a broader distribution in the mountain states and has been confirmed in Colorado, Utah, and Washington. The plant is a perennial, 1–3 feet in height, topped with solitary, cone-shaped pinkish to blue-white flowers (Figure 26.2).

The toxic principle is currently not identified, although a variety of possible compounds have been suggested. The sesquiterpene lactone repin has been investigated. More recently, the compound DDMP (dihydromethylpyrane) has been suggested to be the cause, as it has been shown to be cytotoxic to various regions of the brain.[52] Confirmation of this compound in intoxicated horses or the plants themselves is apparently lacking at the present time.

Clinical signs appear after the horses have had a continuous and protracted ingestion of the plant; occasional consumption does not result in observable clinical abnormalities. Feeding trials suggest that a horse must consume about 59–200% of their body weight (yellow star thistle) or 59–63% of their body weight (Russian knapweed) for a period of 3–11 weeks before clinical signs occur.[53]



Figure 26.2. Yellow star thistle (*Centaurea solstitialis*). Photo courtesy of Dr. Blair Meldrum.



Figure 26.3. Typical lateral curling of the tongue in a horse with nigropallidal encephalomalacia.

It is considered that some horses will actively seek out the plant once exposed to it; it is not usually grazed if more suitable forage is present. Onset of clinical signs is abrupt and the plant primarily affects the muscles of mastication and prehension. Hypertonicity of the facial muscles result in a "wooden" expression, and the mouth is held partially open with the lips retracted. The tongue may be moved but often curls on the side to form a "trough". Horses have a good appetite but cannot move food into the pharynx, hence weight loss develops quickly (Figure 26.3). Horses may immerse their entire head, down to the eyes, in water troughs to drink, and some adopt unusual eating methods, such as "scooping" the feed into their mouths. Circling, depression, yawning, or "frenzied" behavior can be variably seen. Gait deficits appear to be minimal, although conscious proprioceptive deficits may be seen. Death is most commonly due to starvation or dehydration. Animals of all ages can be affected, but younger animals appear to be more susceptible, with a mean age of 2 years reported.[55]

Diagnosis is dependent upon the characteristic clinical signs, combined with the confirmation of access to the toxic plants. Clinicopathologic abnormalities are nonspecific and reflect anorexia and dehydration. Antemortem diagnosis with MRI has demonstrated cavitation of the substantia nigra, but this is not a widely available procedure.[56] Postmortem findings are characteristic, with sharply circumscribed areas of liquefactive necrosis of the substantia nigra or globus pallidus, usually bilaterally symmetrical (Figure 26.4).

There is no specific treatment other than removal from the source of toxin and nursing care. Recovery is unlikely.

Bracken fern

Bracken fern (*Pteridium aquilinum*) is widely distributed across North America, primarily in the northern and western regions. The condition is reported to be well known in the United Kingdom

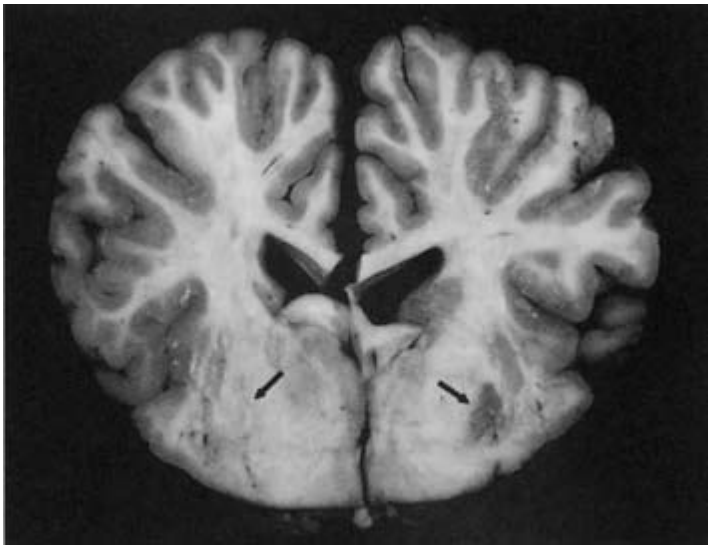


Figure 26.4. Gross post-mortem photograph demonstrating the necrosis of the substantia nigra (arrows) in a horse with nigropallidal encephalomalacia.

and was first reported in Germany in 1897.[57] The plant grows in forested areas and abandoned fields or roadways which are being re-forested. The entire plant is toxic in its natural state or when dried as in hay. Intoxications tend to occur in late summer or fall when forage is limited but can occur at any time of the year. It has been reported that horses can acquire a fondness for the plant and seek it out.[57] Hay containing 20% bracken fern is considered hazardous.[55,57]

The toxic principle of bracken fern is thiaminase, and clinical signs result from the depletion of thiamine. Thiamine is an important cofactor in energy production, catalyzing the decarboxylation of pyruvate to acetyl-CoA.[12] In a group of experimentally poisoned horses, blood thiamine concentration dropped from 8.5 to 1.5 μg/dL, and blood pyruvate concentrations increased from 2.2 to 6.2 mg/dL.[47] Neurologic dysfunction is presumed to arise from cellular energy failure.

The most prominent clinical abnormality associated with bracken fern intoxication is ataxia which begins approximately 1 month after consumption begins, and progresses over several days. All four limbs are typically involved.[57] This maybe associated or preceded by weight loss, and bradycardia and anorexia are usually present.[55,58] If ingestion continues, muscle fasciculations and tremors progressing to terminal convulsions may be seen. Clinical signs and progression are similar to experimentally induced thiamine deficiency using amprolium; however, blindness was also seen in the horses of that report.[55,59] A "tucked-up" appearance with an arched back are commonly reported and appear to be a consistent clinical observation.

Diagnosis is established by the observation of consistent clinical signs (i.e., ataxia of all four limbs with bradycardia and muscle tremors) combined with the observation of bracken fern in the diet. It must be noted, however, that clinical signs can occur for a period of time after bracken is removed from the diet. There are no pathognomonic clinicopathologic changes on routine laboratory analysis. Decreased blood thiamine and RBC transketolase concentrations (a surrogate for thiamine assay) and increased blood lactate and pyruvate concentrations are expected.

Treatment is removal of bracken from the diet, and administration of thiamin intramuscularly (0.25–0.50 mg/kg BW once per day). A loading dose of 5–10 mg/kg of thiamine can be given on the first day of treatment, but this should be diluted in fluids and given slowly, due to the reported potential for adverse reactions.[12] Oral thiamin can also be given orally at 0.5 to 1 g twice per day.[58] Thiamine replacement therapy is reported to provide rapid resolution of clinical signs in naturally occurring disease, but slower return to normalcy (5–7 days) was seen in amprolium-induced thiamine deficiency.[59] Treatment is usually successful if treatment begins

prior to the terminal phase of muscle tremors and convulsions. Necessary duration of treatment apparently depends upon the severity of the condition, but several doses may be needed before complete resolution is achieved.

A similar syndrome is observed following intoxication with *Equisetum arvense* (horse tail, scouring rush), which also produces a thiaminase.[60] This plant remains toxic in hay, but is generally considered unpalatable otherwise.[55] Diets containing 20% *E. arvense* fed for two weeks has been adequate to induce disease.[60] Treatment and management is as for bracken fern.

Hypochoeris Radicata

Stringhalt has been recognized in the horses for centuries and has been described as having one of the two forms: the conventional or classic form of the disease and Australian stringhalt (AS). The classic form of the disease is considered to occur worldwide and is defined by its clinical signs with little other information available. Surgery is usually curative.[61,62] AS was traditionally reported in Australia and New Zealand associated with ingestion of the weed *Hypochoeris radicata* (flatweed);[63] however, this form of stringhalt has been reported in North America.[62,64]

The plant is an invader of disturbed soils and is often seen in stressed pastures. While originally described in Australia and New Zealand, flatweed is widely distributed in North America, particularly the Pacific Northwest, California and Northeastern United States.[62,65] Flatweed is very similar in appearance to the common dandelion, the major difference being that flatweed has a solid stalk and the stalk of the common dandelion is hollow.[62]

Horses with stringhalt demonstrate a very characteristic gait, the severity of which is variable. The syndrome is characterized by exaggerated hock flexion varying from stiffness, which is only seen during periods of excitation, to a marked flexion in which the foot of the affected leg strikes the abdomen. With classic stringhalt, only one leg may be affected, and no other clinical signs are seen. With the Australian form, signs are usually bilateral. Horses sometimes are almost unable to move forward without "bunny-hopping." The rear limbs are most commonly affected, although front limb stiffness can be seen in the Australian (but not classic) form. Recumbency may result in very severe cases. Excitement, turning sharply, going down hill, and prolonged exercise will all exacerbate the gait abnormalities. In addition to gait deficits, laryngeal hemiplegia was observed in 10 of 11 horses with AS.[63] The severity of clinical signs with AS is variable, and a grading scale has been described. Muscle atrophy of the long and lateral digital extensor muscles is most commonly observed, although generalized hindlimb muscle atrophy has been seen.[63]

Most cases of AS have been associated with the ingestion of *H. radicata* (flatweed, false dandelion) although other plants have been suggested including *Taraxicum officinal* and *Lathyrus* species. The toxic principle is not identified and may be a mycotoxin. *H. radicata* has a worldwide distribution, including North and South America, Europe, Australia, New Zealand, and Japan.[61,66] Intoxication tends to occur in situations in which there are large amounts of the weed (>30% of available forage), which occurs in situations of severely overgrazed pastures, often in late summer or fall.[64] Outbreaks with a large number of affected individuals or sporadic cases can be seen. The duration of time to the onset of signs is not clearly established, but it takes at least 2 weeks, and signs may progress, once noted, particularly if consumption continues.[63]

AS is a distal axonopathy, and affected horses demonstrate axonal degeneration and demyelination. This is responsible for the clinical signs seen of peripheral neuropathy (neurogenic muscle atrophy, laryngeal hemiplegia). The pathogenesis of the gait deficit is more complex and probably involves disruption of the reflex arc responsible for motor tone, with damage leading to the disinhibition of upper motor neurons.

Diagnosis is made by observation of the characteristic clinical signs, which are clear in the severe form. Neurologic deficits consistent with hypertonicity and hyperflexion, involving both rear limbs, associated with laryngeal hemiplegia and exposure to the plant are adequate to confirm the diagnosis. EMG will reveal spontaneous electrical activity of the affected muscles, positive sharp waves, and fibrillation potentials, suggesting denervation.[64] Nerve conduction studies find a marked reduction in nerve conduction and a decremental response to repetitive nerve stimulation.[63] Clinicopathologic evaluation

is normal as are serum vitamin E and selenium concentrations. Pathologic examination will reveal peripheral nerve degeneration and muscle atrophy, and spinal cord, brain, or brainstem pathology is not observed.

Treatment primarily involves removal of the horse from the source of toxin, and in cases of AS this appears to result in some resolution of clinical signs, although this usually takes many months and recovery is often incomplete.[63] A 1-week course of treatment with thiamine has been advocated, but results appear to be inconsistent, and it is difficult to attribute clinical improvement to the treatment.[63,64] In addition, phenytoin (15 mg/kg BW per os sid) for 3 weeks has been advocated, also with inconsistent results.[64] Better results were reported with a dosage of phenytoin of 15 mg/kg BW bid);[67] however, the effectiveness of this therapy remains unconfirmed.[66] Treatment with the centrally acting muscle relaxant mephenisin has been reported but with equivocal results.[68] Some success has been reported with the use of the GABA inhibitor baclofen (1 mg/kg tid),[67] but it had no effect in another report.[66]

Leukoencephalomalacia

Equine leukoencephalomalacia (ELEM) (moldy corn disease, cornstalk disease) has been recognized for many years. Reference to it can be found in literature of the 19th century. The association with moldy corn has been known since 1902, when a feeding trial of affected corn resulted in clinical signs consistent with the natural outbreak.[69] Outbreaks have been reported in which large numbers of horses died; up to 5,000 horses died in Iowa during 1934–1935.[70] Even though the cause has been recognized for more than a century, outbreaks still occur, with one fairly recent outbreak resulting in the death of 14 horses of a group of 66, and another resulting in the death of 6 out of 10 horses on another farm.[71,72] The attack rate on any particular farm varied from 14 to 41% in one summary report, with a case fatality rate ranging from 26 to 100%.[73]

The disease is most commonly reported in the eastern and midwestern United States; however, it appears to have a worldwide distribution.[74–76] The toxin is elaborated primarily by *Fusarium moniliforme* and *Fusarium proliferatum*.[77–79] The toxic principle is the mycotoxin fumonisin, of which fumonisin B1 is the most commonly reported, although fumonisin B2 and B3 have been shown to be present in contaminated corn and will cause the same clinical syndrome.[72,78] Fumonisin B1 and B2 appear to have similar toxic potential, although fumonisin B3 is much less toxic.[77] Intoxication is almost exclusively associated with the contamination of corn, and both white and yellow varieties appear to be affected. Environmental conditions which favor toxin production include a period of drought during the growing season with cool moist conditions during pollination and kernel formation.[77] Infected corn may be fed directly or can be part of a grain mix or pelleted feed.[73] There is poor correlation between the concentration of toxin in feed and the visual appearance of the grain.[80]

The toxin acts by inhibiting the synthesis of sphingosine from sphinganine via inhibition of ceramide synthetase.[77,78,81] As a result, the ratio of sphinganine to sphinogosine rises several fold and may be useful in the early detection of intoxication. Clinical signs are presumed to result from this alteration of sphingolipid metabolism. In addition, fumonisin B1 has been shown to alter the permeability of porcine endothelial cells.[81] If a similar phenomenon occurs in equine endothelial cells, this could explain the protein exudation and edema which occurs in the CNS with fumonisin intoxication.

Horses appear to be the most sensitive to the effects of the fumonisin toxin, with concentrations as low as 8–10 ppm resulting in clinical disease.[82] Clinical signs of intoxication occur abruptly, usually after 7–10 days of high dose of the toxin or prolonged ingestion of a low dose of the toxin.[77] Higher doses of toxin favor hepatotoxicity, while chronic ingestion of lower concentrations is more associated with neurologic disease.[77]

Clinical signs of fumonisin neurotoxicosis include the abrupt onset of depression, blindness, and ataxia. Clinical signs rapidly progress to hyperexcitability, headpressing, and delirium. Fumonisin B1 demonstrates dose-dependant characteristics, and when given intravenously at 0.01 mg/kg body weight, no clinical signs are seen. At a dose of 0.05 mg/kg body weight, however, horses developed recognizable neurologic signs 8–13 days after dosing began.[83] These signs included tongue weakness, ataxia, mentation changes, and proprioceptive abnormalities. Mentation changes progressed in some horses to intermittent dementia. More severe signs were seen at higher doses.[83] Sudden death can be observed without prior recognition of neurologic disease.

Clinical signs reflect severe forebrain disease which must be differentiated from viral encephalitis, meningitis or cerebral abscessation, parasitic encephalitis, botulism, hepatoencephalopathy, other intoxications, or trauma. The observation of pink to reddish-brown mold on corn provides presumptive information, although failure to observe this does not rule fumonisin intoxication out. Clinical chemistry analysis of blood may reveal alterations in liver enzymes as well as other nonspecific changes associated with recumbency, stress, or dehydration. Direct fumonisin assay of body fluids does not appear to have value and is not routinely done in clinical cases.

CSF evaluation recovers fluid which is xanthochromic, with an elevated total protein count. A mean CSF total protein concentration of 197 mg/dL was found in 10 horses with neurologic signs after intravenous dosing with fumonisin B1.[83] CSF RBC counts were mildly increased compared to normal controls (12 RBC/μl vs 0.0), but this difference did not achieve statistical significance.[83] CSF nucleated cell counts appear to be variable, and may be normal or increased, presumably associated with the severity of the CNS necrosis.[72,83,84]

Postmortem examination finds widespread softening and liquefactive necrosis of cerebral white matter. Lesions vary in size from very small to large cavitations and are not typically symmetric or bilateral. Lesions may also be seen in the thalamus, brain stem, and medulla. Histologic analysis finds loss of cerebral architecture, primarily white matter necrosis, and perivascular cuffing and proliferation of macrophages (Figure 26.5).[77] Lesions of the liver may be seen with hepatomegally and a brownish discolored liver with irregular foci throughout.[77] Histopathologic changes include hepatocyte vacuolation, periacinar necrosis, portal fibrosis, and bile duct proliferation.[77]

No specific treatment exists, and supportive care is the only option. Treatment with oral laxatives and/or activated charcoal is not of value due to the long duration of intake necessary for toxicity. The prognosis is grave for severely affected horses although mildly affected horses have been known to recover. Prevention involves the avoidance of poorly stored grains (humidity greater than 15%) or those with any questionable appearance. The US Department of Agriculture recommends that feeds contain no more than 5 ppm of fumonisin.

Paspalum staggers

The ergot *Claviceps paspali* infects the seed head of dallis grass (*Paspalum dilatatum*) or bahia grass (*Bahia oppositifolia*). Dallis grass is primarily a warm season grass cultivated in the humid regions of southeastern United States. Toxins produced by the sclerotium of *C. paspali* include a group of compounds that are derivatives of lysergic acid and are collectively referred to as paspalitrems.[77,85] This group is composed of paspalinine, paspalitrem A and paspalitrem B.[85] The toxin apparently interferes with the release of the inhibitory neurotransmitter GABA.[85] Loss of inhibitory neurotransmission results in prolonged depolarization facilitating motor end plate activity, which is the ultimate cause of the observed clinical signs.[77]



Figure 26.5. Cerebral necrosis in the brain of a horse with equine leukoencephalomalacia. (Wilson T. 1990. Fumonisin B1 levels associated with an epizootic of equine leukocencephalomalacia. J Vet Diag Invest 2: 213–6). Reprinted with permission.

Clinical signs associated with the ingestion of the paspalitrems are fine muscle tremors of the head and neck. Stiffness, ataxia, hypermetria, gross muscle tremors, opisthotonus, and seizures may develop. These are particularly noticeable when the horse becomes agitated or excited and may subside if the horse is not handled or stressed.

Diagnosis is based upon observation and elimination of other possible causes, associated with the presence of the ergot sclerotium on seed heads. Clinicopathologic examination is unremarkable, showing only nonspecific changes associated with recumbency. No gross or histologic changes are reported in horses. There is no specific antidote, and signs usually resolve within 1–3 weeks after removal from the infected pasture. Control measures include mowing of pastures to remove the infected seed heads.

Ryegrass staggers

CNS abnormalities associated with the grazing of ryegrass pastures have been recognized in North America, particularly the pacific northwest, Australia, New Zealand, and Europe. Intoxication is the result of infection of the grass with the endophytic fungus *Neotyphodium lolii*, which produces a group of neurotoxic tremorgens known as lolitrem A, B, C, and D.[77] Hot, dry weather with drought stress and overgrazing are the characteristic situation in which this condition is seen. Toxicosis is reported to occur most commonly after a heavy dew or light rain interrupts the dry conditions.[77] Concentrations of the toxin are greatest in the seed; however, the toxin also concentrates in the lower 2 cm of the stem, making ingestion during periods of overgrazing or draught likely.[77,86] A dose of 2 μg/g of dry matter is considered to cause toxic signs.[77]

The toxic principle (lolitrems A–D) causes toxicity by interfering with the release of the inhibitory neurotransmitter GABA, as do the paspalitrems. The clinical signs are the same as that seen in the paspalitrems, specifically fine muscle tremors of the head and neck progressing to stiffness, ataxia, hypermetria, gross muscle tremors, opisthotonus, and seizures in severe cases. Morbidity in affected herds is typically greater than 50% with a low mortality (<10%). Most animals recover within 1 week after removal from the affected premise. Diagnosis is by observation of infected grass, presence of appropriate clinical signs, and elimination of other possible causes. No specific clinicopathological changes are observed, and there are no characteristic postmortem findings. Analysis of affected forage for the presence of the endophyte can be performed.

Locoweed (locoism)

A large variety of plants of the *Astragalus* and *Oxytropis* genera have been incriminated in a CNS disorder of the horse known as locoism. There are over 300 species of *Astragalus* alone and not all cause CNS disease, although many have been incriminated.[12,55] In addition to CNS disease, plants of this genera can cause selenosis and methemaglobinemia, although primarily in cattle. Locoweed is widely distributed in North America from western Canada as far south as northern Mexico and predominately within the western states.[12]

Clinical signs can be seen as quickly as two weeks after ingestion of the plant begins but may take as long as 2 months to be expressed. Although the plant is considered to be unpalatable, once horses do begin to consume it, they seek it out and eat it preferentially.

The ingestion of locoweeds by horses leads to clinical signs of a slow staggering gait, depression, weight loss, ataxia, and anxiety/nervousness. Changes in behavior are noted, in that the horse may separate itself from the herd and become difficult to handle and unpredictable. Gait abnormalities may become exacerbated with excitement. Difficulty in eating and drinking can be seen as well as blindness in some cases. Abortion can be seen in pregnant mares as well as the birth of foals with a variety of limb deformities.

The toxic principle, swainsonine, inhibits alpha-mannosidase, a lysosomal enzyme required for the metabolism of oligosacharides.[55] This metabolic disruption leads to the formation of intracytoplasmic vacuoles, which will result in permanent cell damage if persistent. Consumption for as few as 8 days will result in the presence of vacuoles of neurons within the CNS. Vacuoles will regress if feeding is discontinued early, but if consumption continues, vacuolation leads to cell death. Neurologic signs are a direct result of the disruption of cellular function induced by the presence of the vacuoles in Purkinje cells of the cerebellum and cerebral cortex. Associated weight loss is due to vacuolation of numerous other organs, while blindness is likely due to the vacuolation of cells of the retina.

Diagnosis is based upon the observation of consistent clinical signs and confirmation of access to, and consumption of, the plant. No specific antemortem test has been described, although biopsy of assessable tissues and histologic examination may reveal the characteristic vacuolation. Clinicopathologic testing is nonspecific and may reflect various organ system dysfunction. Vacuolation may be seen in leukocytes, but the value of this observation as a diagnostic is unknown.

Treatment is dependant upon eliminating access of the horse to the plant. This may be difficult in some cases in which the horse seeks out the plant and requires more than simply providing better quality forage. Early recognition and removal from the plant are the key, as mild cases may recover in 1–2 weeks after ingestion ceases. More chronic cases have little chance for full recovery and may have persistent gait or behavioral deficits making them unsafe for use. Death can result from emaciation, and progressively severe neurologic disease may necessitate humane destruction.

Sorghum cystitis

Horses grazing various sorghum species can demonstrate a fairly well-described neurologic syndrome of cystitis and caudal ataxia.[87] Clinical signs are most commonly seen in horses which consume hybrid crosses of sorghum (*Sorghum vulgare*) and sudan grass (*S. vulgare var sudanense*). Other species such as Johnson grass (*Sorghum halepense*) have also been incriminated but less frequently.[88,89] Cases have been described in the western and southwestern states of the United States, as well as in northern and western Australia.[88,90,91] Sudan or Johnson grass hay which has been well cured does not appear to be toxic.[88,89]

Clinical presentation is a symmetric ataxia and weakness of the rear limbs; flaccid paralysis of the legs or tail may develop abruptly. Urinary incontinence (dribbling of urine) soon follows in about one-half of horses with ataxia.[88] A "bunny-hopping" type gait is occasionally seen. Backing exacerbates the clinical signs in the pelvic limbs. Clinical examination is unremarkable with the exception of urine scalding, ataxia, and perhaps a flaccid tail. Examination of the bladder may reveal a sabbulous cystitis which may be severe. Clinicopathologic testing is usually unremarkable. CSF results have not been reported.

Diagnosis is supported by the observation of symmetrical ataxia, signs of cauda equina syndrome, and exposure to appropriate feedstuffs. Differential considerations include sacral fractures, equine protozoal myeloencephalitis, osteomyelitis, and bacterial infections. The work-up and differential considerations for cauda equina syndrome are more fully discussed in Section 2, Chapter 9.

Treatment is supportive, and prompt removal from the toxin source is necessary. Not all horses in an exposed group will be affected; a morbidity of 25% was seen in one study with a mortality of less than 2%.[88,90] Drainage of the bladder associated with irrigation to remove sediment is beneficial to prevent distention-induced trauma to the detrusor muscle and aid in the horses comfort.

The toxic principle associated with sorghum intoxication is unknown; however, it is suspected to be associated with the development of cyanide in the plant during periods of rapid lush growth. Most reported cases were associated with a young, green stage of growth and during seasons of medium to high rainfall.[88] In one report, the grazing period prior to the development of clinical signs varied among affected cases from 1 week to 6 months.[88]

In addition to neurologic disease, fetal abnormalities have been observed in the foals of mares which grazed sorghum. Abortions which may or may not be associated with fetal ankylosis have been observed as well.[88,92]

Postmortem examination usually finds evidence of severe cystitis. Gross changes in the nervous system are not observed; however, histologic examination finds axonal degeneration and demyelination in the ventral funiculus of the cervical, thoracic, lumbar, and sacral segments of the CNS.[88]

Miscellaneous plant intoxications

Ingestion of various legumes has resulted in neurologic disorders of horses. Ingestion of laburnum (*Laburnum anagyroides*) seeds (0.6 g/kg BW) resulted in signs of excitement, incoordination, convulsions, and death.[47] Consumption of the legume *Lathyrus nissolia* (grass vetchling) was associated with severe ataxia, which resolved following removal of the source.[47] Consumption of Lathyrus has also resulted in laryngeal paralysis and stringhalt.

The black locust tree (*Robinia pseudoacacia*) has been reported to be toxic to horses when they ate bark or trimmed branches. The toxic principle is the

Table 26.1. Summary of Clinical Signs Associated with Selected Equine Neurotoxins

Toxin/Syndrome	CNS Stimulation	CNS Depression	Spinal Cord Signs	Peripheral Neuropathy	Muscle Fasciculations	Miscellaneous
Bracken fern			+++		+	Bradycardia, seizures
Carbamates	+		+		+	Colic, bradycardia
Fluphenazine	+++				+	
Haloxon				+		Roaring
Hypochorius			+++	+		roaring
Ionophore		+++	+			sweating
Ivermectin		+	+			Blindness
Lead			+	+++		Dysphagia, roaring
Levamisol	+++				+	
Locoism	+++		+++		+	Weight loss, blindness
Mercury			+++	+++		Dermatitis, weight loss
Metaldehyde	+++				+	seizures
Moldy corn	+ (seizures)	+++	+++			blindness
Moxidectin		+++	+		+	seizures
Nicotine	+++ (early)	+++ (late)	++		+	tachycardia
Nigropallidal encephalomalacia	+	+				Dysphagia
Organophosphates	+		+		+	Colic, bradycardia
Paspalum staggers	+ (seizures)		+++		+++	
Ryegrass staggers	+ (seizures)		+++		+++	
Sorghum/sudan grass			+++			Cauda equina syndrome
Urea	+++	+++				Dementia

+++ indicates that this is a predominant sign or very commonly seen, while + indicates a less commonly seen clinical sign.

plant lectin robin. Clinical signs include depression, anorexia, weakness, mydriasis, irregular tachycardia, diaphragmatic flutter, and posterior paralysis. Treatment is symptomatic.

The poison hemlock (*Conium maculatum*) is found growing in ditches and along roadways in the cooler climates of the United States. The toxic principle is a group of alkaloids including coniine and *N*-methyl-conine. The pharmacologic action is similar to nicotine, stimulating, then paralyzing autonomic ganglia and neuromuscular junctions.[55] Corneal reflexes are spared, but horses are demented and lose awareness, become recumbent, and die of respiratory failure. The early growth is most palatable, and as few as 5 fresh leaves can intoxicate a horse.[55] The plant is not toxic when dried in hay.[55]

Water hemlock (*Cicuta maculata*) is considered one of the most toxic of all plants. It grows only in wet and swampy areas throughout North America.

The toxic principle is cicutoxin, which is concentrated in the rootstock, which is the most toxic part of the plant. The toxin is a direct CNS stimulant, leading to apprehension, mydriasis, and convulsions. Death can occur within 30 min of ingestion, but horses that survive 5–6 h usually recover.[55]

The western whorled milkweed (*Asclepias subverticillata*) contains neurotoxic cardenolides which can result in CNS stimulation, convulsions, and rapid death. The plant remains toxic when dried, and a lethal dose is considered to be 0.05% of BW dry matter in hay.[55]

A syndrome of hind limb ataxia and limb weakness was noted in horses after long-term grazing of branched onion weed (*Trachyandra divaricata*).[93] This plant is widely distributed in the southwestern regions of South Africa and the southwestern region of Australia. In South Africa, grazing of a related plant, *Trachyandra laxa*, may cause similar signs.[94] In addition to gait deficits, a crouching posture with diffuse muscle fasciculations was noted. Diffuse muscle weakness becomes prominent, and diffuse muscle wasting had been noted in a flock of sheep which had been similarly intoxicated. Gross postmortem does not reveal any abnormalities, but histopathologic examination finds widespread lipofuscin storage in neurons, brain, and spinal cord.[93] In addition, lipofuscin was noted within the neurons of the autonomic ganglia of the gut, possibly explaining the signs of colic in some animals.

There appears to be no specific treatment, and recovery from the condition has not been observed once clinical signs are noted. The toxic principle has not been identified, but it appears that continuous ingestion over several weeks is required for intoxication. Supplementary feeding of good quality forage for animals housed in pastures with the plant is likely to be protective.

Transient ataxia has been noted following contact with stinging nettles (*Urtica dioica*). Caudal ataxia associated with mild agitation and an urticarial rash was observed. The signs resolved with empirical treatment within a few hours.[95]

A syndrome of ataxia and mental dullness is observed in horses in the Queensland area of Australia, known locally and historically as "coastal staggers."[96] The illness is due to the consumption of the plant *Gomphrena celosioides*. It is reported to be common along the coastal strip of Queensland, extending inland up to 300 miles. It grows on embankments along roads and railways and on stressed or fallow land. The plant appears to be palatable and readily eaten by horses; however, considerable quantity is required (5–6 lbs/day for 30 days) before clinical signs of ataxia, mental dullness, and eventual recumbency develop. No specific treatment is known, and there are no reported CNS lesions present.

The summary of clinical signs associated with selected equine neurotoxins is given in Table 26.1.

REFERENCES

1. Brewer B, Hines M, Stewart JT, *et al.* 1990. Fluphenazine induced parkinson-like syndrome in a horse. *Equine Vet J* 22:136–7.
2. Kauffman VG, Soma L, Divers TJ, *et al.* 1989. Extrapyramidal side effects caused by fluphenazine decanoate in a horse. *J Am Vet Med Assoc* 195: 1128–30.
3. Baird JD, Arroyo LG, Vengust M, *et al.* 2006. Adverse extrapyramidal effects in four horse given fluphenazine decanoate. *J Amer Vet Med Assoc* 229:104–10.
4. McCrindle CM, Ebedes H, Swan GE. 1989. The use of long-acting neuroleptics, perphenazine enanthate and pipothiazine palmitate in two horses. *J S Afr Vet Assoc* 60:208–9.
5. Hautekeete LA, Khan SA, Hales WS. 1998. Ivermectin toxicosis in a zebra. *Vet Hum Toxicol* 40: 29–31.
6. Leaning WD. 1983. The efficacy and safety evaluation of ivermectin as a paranteral and oral antiparasitic agent in horses. *Proc Annual Meeting Am Assoc Equine Pract* 29:319–28.
7. Campbell WC, Benz GW. 1984. Ivermectin: a review of efficacy and safety. *J Vet Pharmacol Ther* 7:1–16.
8. Johnson PJ, Mrad DR, Schwartz AJ, *et al.* 1999. Presumed moxidectin toxicosis in three foals. *J Amer Vet Med Assoc* 214:678–80.
9. Khan SA, Kuster DA, Hansen SR. 2002. A review of moxidectin overdose cases in equines from 1998 through 2000. *Vet Hum Toxicol* 44: 232–5.
10. Cruther LR. 1994. Foal safety study. In *Freedom of Information Summary, NADA*. 0876-E-US-4-94. Washington DC: US Food and Drug Administration Center for Veterinary Medicine.
11. Rose RJ, Hartley WJ, Baker W. 1981. Laryngeal paralysis in Arabian foals associated with oral haloxon administration. *Equine Vet J* 13:171–6.
12. Schmitz DG. 1998. Toxicologic Problems. In *Equine Internal Medicine*, edited by Reed S, Bayly W, 981–1042. Philadelphia: W.B. Saunders.

13. Drudge JH, Lyons ET, Swerczek TW. 1974. Critical tests and safety studies on a levamisole-piperazine mixture as an anthelmintic in the horse. *Am J Vet Res* 35:67–71.
14. McClanahan S, Hunter J, Murphy M, *et al.* 1998. Propylene glycol toxicosis in a mare. *Vet Hum Toxicol* 40:294–6.
15. Myers VS, Usenik EA. 1969. Propylene glycol intoxication of horses. *J Amer Vet Med Assoc* 155:1841–3.
16. Dorman DC, Hasheck WM. 1991. Fatal propylene glycol toxicosis in a horse. *J Amer Vet Med Assoc* 198:1643–4.
17. Amend JF, Mallon FM, Wren WB, *et al.* 1980. Equine monensin toxicosis: some experimental clinicopathologic observations. *Compend Contin Educ Pract Vet* 2:S173–S182.
18. Rollinson J, Taylor FG, Chesney J. 1987. Salinomycin poisoning in horses. *Vet Rec* 121:126–8.
19. Blomme EAG, La Perle KM, Wilkins PA, *et al.* 1999. Ionophore toxicity in horses. *Eq Vet Educ* 11:153–8.
20. Shclafer M, Somani P, Pressman BC, *et al.* 1978. Effects of the carboxylic ionophore monensin on atrial contractility and Ca2+ regulation by isolated cardiac microsomes. *J Mol Cell Cardiol* 10: 333–46.
21. Shier WT, Dubourdieu DJ. 1992. Sodium- and calcium-dependant steps in the mechanism of neonatal rat cardiac myocyte killing by ionophores: the sodium-carrying ionophore, monensin. *Toxicol Appl Pharmacol* 116:47–56.
22. Matsuoka T. 1976. Evaluation of monensin toxicity in the horse. *J Am Vet Med Assoc* 169:1098–100.
23. Hanson LJ, Eisenbeis HG, Givens SV. 1981. Toxic effects of lasalocid in horses. *Am J Vet Res* 42: 456–61.
24. Knight HD, Costner GC. 1977. Bromide intoxication of horses, goats, and cattle. *J Am Vet Med Assoc* 171:446–8.
25. Mayhew IG. 1989. Disorders of behavior and personality. In *Large Animal Neurology*, edited by Mayhew IG, 73–112. Philadelphia: Lea and Febinger.
26. Gardner CA, Benetts HW. 1952. Poison plants of western Australia. I. Pituri (*Duboisia hopwoodii* [F. Muell]). *J Dept Agric W Aust, 3rd ser* 1:53–6.
27. Taylor P. 1980. Ganglionic stimulating and blocking agents. In *The Pharmacological Basis of Therapeutics*, edited by Gilman AG, Goodman LS, Gilman A, 211–34. New York: Macmillan Publishing.
28. Seawright AA, Roberts MC, Costigan P. 1978. Chronic methylmercurialism in a horse. *Vet Hum Toxicol* 20:6–9.
29. Roberts MC, Seawright AA, Ng JC. 1979. Chronic phenylmercuric acetate toxicity in a horse. *Vet Hum Toxicol* 21:321–7.
30. Roberts MC, Seawright AA. 1978. The effects of prolonged daily low level mercuric chloride dosing in a horse. *Vet Hum Toxicol* 20:410–5.
31. Shuh JL, Ross C, Meschter C. 1988. Concurrent mercuric blister and dimethyl sulphoxide (DMSO) application as a cause of mercury toxicity in two horses. *Equine Vet J* 20:68–71.
32. Guglick MA, MacAllister CG, Chandra AM, *et al.* 1995. Mercury toxicosis caused by ingestion of a blistering compound in a horse. *J Amer Vet Med Assoc* 206:210–4.
33. Sojka JE, Hope W, Pearson D. 1996. Lead toxicosis in 2 horses: similarity to equine degenerative lower motor neuron disease. *J Vet Intern Med* 10:420–3.
34. Burrows GE. 1982. Lead poisoning in the horse. *Eq Pract* 4:30–6.
35. Aronson AL. 1972. Lead poisoning in cattle and horses following long-term exposure to lead. *Am J Vet Res* 33:627–9.
36. Dollahite JW, Rowe LD, Reagor JC. 1975. Experimental lead poisoning in horses and Spanish goats. *Southwest Vet* 28:40–5.
37. Goyeri RA. 1991. Heavy Metal Toxicities. In *Toxicology*, edited by Amdurr MD, Doull J, Klassen CD, 623–80. New York: Pergamon.
38. McSherry BJ, Willoughby RA, Thompson RG. 1971. Urinary delta amino-levulinic acid (ALA) in the cow, dog, and cat *Can J Comp Med* 35:136–40.
39. Lilly CW. 1985. Strychnine poisoning in the horse. *Eq Pract* 7:7–10.
40. Harris WF. 1975. Metaldehyde poisoning in three horses. *Mod Vet Pract* 56:336–7.
41. Sutherland C. 1983. Metaldehyde poisoning in horses. *Vet Rec* 112:64.
42. Edwards HG. 1986. Methiocarb poisoning in a horse. *Vet Rec* 119:556–7.
43. Alexander KA. 1987. Methiocarb poisoning in a horse. *Vet Rec* 120:47–8.
44. Ray AC, Dwyer JN, Fambro GW. 1978. Clinical signs and chemical confirmation of 4-aminopyridine poisoning in horses. *Am J Vet Res* 39: 329–340.
45. Auer DE, Seawright AA, Pollitt CC, *et al.* 1984. Illness in horses following spraying with amitraz. *Aust Vet J* 61:257–9.
46. Olson CT, Keller WC, Gerken DF, *et al.* 1984. Suspected tremetol poisoning in horses. *J Amer Vet Med Assoc* 185:1001–3.
47. Hahn CN, Mayhew IG, MacKay R. 1999. Nervous system. In *Equine Medicine and Surgery*, edited by Colahan PT, Mayhew IG, Merritt AM, Moore JN, 863–996. St. Louis: Mosby.

48. Larson KA, Young S. 1970. Nigropallidal encephalomalacia in horses in Colorado. *J Amer Vet Med Assoc* 156:626–8.
49. Fowler ME. 1965. Nigropallidal encephalomalacia in the horse. *J Amer Vet Med Assoc* 147:607–16.
50. Young S, Brown WW, Klinger B. 1970. Nigropallidal encephalomalacia in horses fed russian knapweed (*Centaurea repens L.*). *Am J Vet Res* 31: 1393–404.
51. Farrell RK, Sande RD, Lincoln SD. 1971. Nigropallidal Encephalomalacia in a Horse. *J Amer Vet Med Assoc* 158:1201–4.
52. Talcott P. 2003. Nigropallidal encephalomalacia. In *Current Therapy in Equine Practice*, edited by Robinson NE, 780–1. Philadelphia: Elsevier Science.
53. Young S, Brown WW, Klinger B. 1970. Nigropallidal encephalomalacia in horses caused by ingestion of weeds of the genus *Centaurea*. *J Amer Vet Med Assoc* 157:1602–6.
54. Gard GP, de Sarem WG. 1973. Nigropallidal encephalomalacia in horses in New South Wales. *Aust Vet J* 49:107–8.
55. Barr AC, Reagor JC. 2001. Toxic Plants. In *The Veterinary Clinics of North America; Equine Practice*, edited by Turner AS, 17:529–46. Philadelphia: W.B. Saunders.
56. Sanders SG, Tucker RL, Bagley RS, *et al.* 2001. Magnetic resonance imaging features of equine nigropallidal encephalomalacia. *Vet Rad Ultra* 42: 291–6.
57. Evans ETR, Evans WC, Roberts HE. 1951. Studies on bracken poisoning in the horse. *Br Vet J* 107: 364–71.
58. Evans ETR, Evans WC, Roberts HE. 1951. Studies on bracken poisoning in the horse. II. *Br Vet J* 107:399–411.
59. Cymbaluk NF, Fretz PB, Loew FM. 1978. Amprolium-induced thiamine deficiency in horses: clinical features. *Am J Vet Res* 39:255–61.
60. Henderson JA. 1952. The antithiamine action of *Equisetum*. *J Amer Vet Med Assoc* 120:375–8.
61. Fintl C. 2003. Idiopathic and rare neurologic diseases. In *Current Therapy in Equine Medicine*, edited by Robinson NE, 760–3. Philadelphia: Saunders.
62. Gay CC, Fransen S, Richards J, *et al.* 1993. Hypochoeris-associated stringhalt in North America. *Equine Vet J* 25:456–7.
63. Huntington PJ, Jeffcoat LB, Friend SC, *et al.* 1989. Australian Stringhalt—epidemiological. clinical and neurological investigations. *Equine Vet J* 21:266–73.
64. Gardner SY, Cook AG, Jortner BS, *et al.* 2005. Stringhalt associated with a pasture infested with *Hypochoeris radicata*. *Equine Vet Ed/AE* 7: 154–8.
65. Galey FD. 1991. Outbreaks of Stringhalt in Northern California. *Vet Hum Toxicol* 33:176–7.
66. Takahashi T, Kitamura M, Endo Y, *et al*. 2002. An outbreak of stringhalt resembling Australian stringhalt in Japan. *J Equine Sci* 13:93–100.
67. Whitton RC, Hodgson DR, Rose RJ. 2000. Musculoskeletal system. In *Manual of Equine Practice*, edited by Rose RJ, Hodgson DR, 95–185. Philadelphia: W.B. Saunders.
68. Cahill JI, Goulden BE, Pearce HG. 1985. A review and some observations on stringhalt. *N Z Vet J* 33: 101–4.
69. Butler T. 1902. Notes on a feeding experiment to produce leucoencephalitis in a horse with positive results. *Amer Vet Rev* 26:748–51.
70. Graham R. 1936. Cornstalk disease investigations: toxic encephalitis or non-virus encephalomyelitis of horses. *Vet Med* 31:46–50.
71. Wilson TM, Ross F, Rice LG, *et al.* 1990. Fumonisin B1 levels associated with an epizootic of equine leukoencephalomalacia. *J Vet Diagn Invest* 2:213–6.
72. Wilkins PA, Vaala WE, Vivotofsky D, *et al.* 1994. A herd outbreak of equine leukoencephalomalacia. *Cornell Vet* 84:53–9.
73. Wilson TM, Nelson PE, Marasis WF, *et al.* 1990. A mycological evaluation and *in vivo* toxicity evaluation of feed from 41 farms with equine leukoencephalomalacia. *J Vet Diagn Invest* 2:352–4.
74. Shier WT. 2000. The fumonisin paradox: a review of research on oral bioavailability of fumonisin B1, a mycotoxin produced by *Fusarium moniliforme*. *J. Toxicol-Toxin Reviews* 19:161–87.
75. Salles-Gomez TL, Almeida PE, Moreira M, *et al.* 2003. Equine leucoencephalomalacia caused by commercial horses ration with fumonisin concentration lower than 10 ppm. *ARS Veterinaria* 19: 267–71.
76. Marasas WF, Kellerman TS, Gelderblom WCA, *et al.* 1988. Leukoencephalomalacia in a horses induced by fumonisin B1 isolated from *Fusarium moniliforme*. *Onderstepoort J Vet Res* 55:197–203.
77. Osweiler GD. 2001. Mycotoxins. In *Veterinary Clinics of North America: Equine Practice*, edited by Turner AS, 17:547–66. Philadelphia: W.B. Saunders.
78. Riley RT, Showker JL, Owens DL, *et al.* 1997. Disruption of sphingolipid metabolsim and induction of equine leukoencephalomalacia by *Fusarium proliferatum* culture material containing fumonisin B2 or B3. *Exp Tox Pharmacol* 3:221–8.
79. Ross PF, Nelson PE, Owens DL, *et al.* 1994. Fumonisin B2 in cultured *Fusarium proliferatum*,

M-6104, causes equine leukoencephalomalacia. *J Vet Diagn Invest* 6:263–5.
80. Binkerd KA, Scott DH, Everson RJ, *et al.* 1993. Fumonisin contamination of the 1991 Indiana corn crop and its effects on horses. *J Vet Diagn Invest* 5:653–5.
81. Ramasamy S, Wang E, Hennig B, *et al.* 1995. Fumonisin B1 Alters Sphingolipid Metabolism and Disrupts the Barrier Function of Endothelial Cells in Culture. *Toxicol Appl Pharmacol* 133: 343–8.
82. Wilson TM, Ross PF, Owens DL, *et al.* 1992. Experimental reproduction of ELEM. *Mycopathologia* 117:115–20.
83. Foreman JH, Constable PD, Waggoner AL, *et al.* 2004. Neurologic abnormalities and cerebrospinal fluid changes in horses administered fumonisin B1 intravenously. *J Vet Intern Med* 18:223–30.
84. McCue P. 1989. Equine Leukoencephalomalacia. *Compend Contin Educ Pract Vet* 11:646–51.
85. Plumlee KH, Galey FD. 1994. Neurotoxic Mycotoxins: a review of fungal toxins that cause neurological disease in large animals. *J Vet Intern Med* 8:49–54.
86. Galey FD, Tracy M, Craigmill AL, *et al.* 1991. Staggers induced by consumption of perennial ryegrass in cattle and sheep from northern California. *J Amer Vet Med Assoc* 199:466–70.
87. Roman WM, Adams LG, Bullard TL, *et al.* 1966. Cystitis syndrome of the equine *Southwest Vet* 19:95–9.
88. Adams LG, Dollahite JW, Romane WM, *et al.* 1969. Cystitis and ataxia associated with sorghum ingestion by horses. *J Am Vet Med Assoc* 155: 518–24.
89. Hahn CN, Mayhew IG, MacKay RJ. 1999. Diseases of the cauda equina. In *Equine Medicine and Surgery*, edited by Colahan PT, Merritt AM, Moore JN, Mayhew IG, 972–5. St. Louis: Mosby.
90. vanKampen KR. 1970. Sudan grass and sorghum poisoning of horses: a possible lathyrogenic disease. *J Amer Vet Med Assoc* 156:629–30.
91. Knight PR. 1968. Equine cystitis and ataxia associated with grazing of pastures dominated by sorghum species. *Aust Vet J* 44:257.
92. Prichard JT, Voss JL. 1967. Fetal ankylosis in horses associated with hybrid Sudan pasture. *J Amer Vet Med Assoc* 150:871–3.
93. Huxtable CR, Chapman HM, Main DC, *et al.* 1987. Neurological disease and lipofuscinosis in horses and sheep grazing *Trachyandra divaricata* (branched onion weed) in south Western Australia. *Aust Vet J* 64:105–8.
94. Grant RC, Basson PA, Kid AB. 1985. Paralysis and lipofuscin-like pigmentation of farm stock caused by the plant *Trachyandra laxa var. laxa. Onderstepoort J Vet Res* 52:255.
95. Bathe AP. 1994. An unusual manifestation of nettle rash in three horses. *Vet Rec* 134:11–2.
96. Newton LG. 1952. *Gomphrena celosioides*–A plant causing ataxia in horses. *Aust Vet J* 28:151–4.

27
Hypoxic/Ischemic Encephalopathy in the Foal

Martin Furr

INCIDENCE/OCCURRENCE

Noninfectious encephalopathy of neonatal foals has been referred to by a variety of terms which either describe the clinical signs or the putative pathophysiology. Hence, the terms hypoxic/ischemic encephalopathy (HIE), neonatal maladjustment syndrome (NMS), "barkers," "dummies," "wanderers," and "convulsives" have all been used. Based upon similar syndromes of neonatal encephalopathy in human infants, hypoxic and ischemic damage to the central nervous system (CNS) has been considered to be the most likely cause. Some veterinarians, however, point out that extrapolation from humans is not necessarily appropriate and no research has demonstrated this particular mechanism of action in foals and hence, prefer to simply refer to this syndrome as "neonatal encephalopathy." Given the similarity of clinical signs, epidemiological evidence, and association of the illness with documented perinatal asphyxia in clinical cases, it is most likely, however, that the combined effects of hypoxia and ischemia (perinatal asphyxia) are involved, and the term HIE will be used in this chapter. Perinatal asphyxia is commonly recognized in human neonatal intensive care units and is becoming more recognizable in equine neonatal units. It is difficult to determine the actual incidence of perinatal asphyxia or HIE because many foalings are unattended, and perinatal asphyxia is often complicated by other conditions which make recognition difficult. However, one study reported that 52% of foal deaths associated with "respiratory disease" were directly caused by asphyxia.[1] Another study has reported that complications of birth, including dystocia and neonatal asphyxia, were responsible for 19% of the 3,514 foal deaths at less than 24 h of age.[2] Clearly, perinatal asphyxia is a significant cause of equine neonatal morbidity and mortality. Hypoxic ischemic encephalopathy is reported as "a common problem" in horse breeding areas[3] and was identified as the cause of death in 14% of foals less than 7 days of age in one study.[4]

ETIOLOGY AND PATHOPHYSIOLOGY

A number of different pathophysiologic mechanisms have been suggested over the years as the cause of HIE in foals. Premature clamping or rupture of the umbilical cord, with subsequent "blood deprivation" to the foal has been suggested and discussed for many years.[5] While the authors reported that up to 1,500 mL of blood could be lost from a prematurely severed umbilical cord, subsequent work has not confirmed the result and in fact demonstrate no progressive blood flow in the umbilical cord, nor any change in the hematology of foals with early cord separation.[6] Hence, the effect of premature clamping or severance of the cord on the development of HIE are probably of very minor importance. Other suggestions have been that dynamic changes in vascular pressures and flow in the head of the foal may be associated.[7] These observations have not been pursued, but initial efforts did not appear to support the concept. Further, the observation of intracranial hemorrhage in foals delivered by caesarian section would appear to invalidate this concept.[8] Some authors have stated that HIE is most often associated with rapid, uncomplicated delivery[9], yet HIE is also clearly seen in many clinical settings which can result in hypoxia of the fetus, such as dystocia, intrauterine

umbilical cord compression, decreased placental blood flow, and premature placental separation. These observations, as well as extrapolation from human medicine, provide strong evidence that the pathophysiology must involve hypoxia and ischemia although not excluding the possibility that other factors also contribute.

Asphyxia is defined as a reduction of tissue oxygenation, which can result from hypoxemia (decreased oxygen content of blood) or ischemia (decreased blood flow and tissue perfusion). Perinatal asphyxia is found in a wide variety of clinical settings which result in decreased umbilical blood flow, uteroplacental perfusion, or tissue oxygenation. Fetal factors, dystocia, placental abnormalities, and maternal illness may all be involved. Additionally, more than one of the above factors may be involved in an individual case.

However it is induced, asphyxia initiates a series of events in the CNS which result in brain damage and dysfunction. Key elements include energy failure, altered neurotransmitter metabolism, altered calcium metabolism, and alteration in cerebral blood flow (CBF), all culminating in neuronal cell death. The primary event is an oxygen deficit, arising from both hypoxia and ischemia. Numerous studies have examined the effects of oxygen deficit upon energy metabolism. Early changes are a decrease in brain glycogen concentration and an increase in lactate (after 2 min of anoxia). Lactate accumulates when glucose is metabolized in the absence of oxygen. High energy phosphate compounds (i.e., adenosine triphosphate (ATP)) begin to decrease after 2 min of anoxia and are reduced by 30% after 6 min.[10] While both hypoxia and ischemia will lead to similar effects, the effects of each are magnified when both are present.

These effects are "universal;" however, age seems to have a large effect upon the response. Neonates are clearly more resistant to the effects of hypoxia.[10] The reasons for this resistance are numerous and include the following:

1. lower rate of energy utilization
2. lower rate of accumulation of toxic products
3. increased utilization of lactate
4. preservation of cardiovascular function in neonates.

While decreased carbohydrate concentrations in the brain exist, the effects of glucose concentration upon brain injury are confusing.[11] Hyperglycemia results in greater severity of brain injury in the adult, whereas hyperglycemia in the neonatal rat is protective.[12] Other investigators have concluded that hyperglycemia is not protective, however, even in neonates.[13] Differences in reported results probably reflect subtle differences in methodology, species or strain, and methods of determining damage. No such work has been reported in the horse.

In summary, it is important to recognize that a fundamental component of brain injury following hypoxia/ischemia is energy failure. This energy failure has a number of consequences which directly lead to neuronal cell death. The energy failure needed to induce these events, however, appears inadequate to be the sole cause of neuronal death.

Role of Neurotransmitter Metabolism

Alteration in neurotransmitters (particularly glutamate) and its receptors have particular importance in the pathophysiology of brain damage resulting from hypoxia/ischemia. In normalcy, glutamate is released from the axon terminus, and it interacts with one of two types of glutamate receptors: ionotropic (NMDA, AMPA, and kainate) and metabotropic (phosphoinositide hydrolysis, protein C activation). Excessive glutamate in the synapse and surrounding tissues is absorbed by the nearby astrocytes, which metabolize the glutamate back to glutamine. AMPA receptors mediate the flux of sodium (Na) and potassium (K), while NMDA receptors mediate the flux of Na, K, and Ca. In addition, Ca will induce the release of glutamate at the presynaptic membrane. In conditions of hypoxia and ischemia, and hypoglycemia, glutamate release is increased with the end result being accumulation of glutamate. This arises due to (1) increased release from persistent depolarization, (2) loss of GABAergic inhibitory neurons, and (3) blockade of inhibitory neurons (in neonates, at least).

These effects are important because glutamate is particularly toxic to neurons *in vitro* at concentrations (500 μmol/L) that can be achieved and demonstrated *in vivo*.[10] The observation that inhibition of glutamate receptors is protective to hypoxia-induced brain damage lend support to this purported role. There are two forms of cell death associated with glutamate. One is a rapid cell death due to massive Na influx followed by water with subsequent cell swelling and death. Delayed cell death

occurs due to the effects of increased intracellular Ca. Most cell deaths occur in the period after which the insult has been corrected.

Role of Calcium

Normal cellular metabolism of Ca is of crucial importance. In normalcy, the cytosolic Ca concentration is kept very low by several mechanisms. There are plasma membrane voltage dependant channels (VDCC), two agonist dependant channels (NMDA and metabotropic receptors), ATP dependant uniporters, the endoplasmic reticulum, and the mitochondrion.

Failure of ATP-dependant uniporters leads to increased cytosolic Ca. In addition, energy failure leads to release of Ca from mitochondrion and endoplasmic reticulum. Depolarization of the membrane results in Ca influx via VDCC. Further, stimulation of the NMDA receptor (via glutamate) leads directly to Ca influx. Additionally, stimulation of the glutamate metabotropic receptor stimulates the release of IP3, which directly stimulates the release of Ca from the endoplasmic reticulum. The end result being increased cytosolic (but not necessarily blood) Ca concentrations. Increased cytosolic Ca has a number of deleterious effects which ultimately lead to the death of the cell (Table 27.1).

Altered Blood Flow

Asphyxia results in major circulatory effects. The initial effect is a redistribution of cardiac output with subsequent increase in CBF, followed by a rapid loss of cerebral autoregulation (i.e., the ability to maintain normal blood flow over a range of perfusion pressures). Later effects include decreased cardiac output and hypotension with a decreased CBF. Seizure activity is known to increase CBF and induce hypertension and is felt to contribute to CNS parenchymal bleeding. CBF is also important in the post-asphyxial period. In experimental models of asphyxia in newborn lambs, cerebrovascular autoregulation is lost when the partial pressure of oxygen in arterial blood (PaO_2) changed from 70 to 30 mm Hg. This loss of autoregulation occurred after only 20 min of partial asphyxia and did not return until 7 h after restoring normoxemia.[10] Systemic acidosis also caused a loss in cerebrovascular autoregulation.[10] While similar data have not been generated for neonatal foals, it is reasonable to assume that the responses are similar and have important consequences for treatment of the neonatal foal with HIE.

Neuronal Cell Death

From the foregoing discussion, one can summarize the events which lead to neuronal cell death. Free radicals produced during hypoxic/ischemic damage of the brain cause peroxidation of membrane phospholipid leading to breakdown of the cell membrane and cellular death. Energy depletion induces a number of metabolic changes within the cell leading to neuronal cell death (Figure 27.1). Energy depletion increases membrane depolarization and cytosolic Ca. These changes will subsequently increase glutamate release, which promotes further depolarization and intracellular Ca and cellular swelling.[14] Both glutamate and Ca are cytotoxic.

CLINICAL SIGNS

The clinical signs of HIE in foals are varied and reflect diffuse cerebrocortical disease. The clinical signs are usually observed in the first 24 h of life but

Table 27.1. Effects of Calcium upon Cellular Metabolism

Calcium Effect	Deleterious Effects
Activates phospholipases	Phospholipid hydrolysis
Stimulates arachidonic acids and free radicals	
Activates proteases	Cytoskeletal disruption
Activates nucleases	Nuclear injury
Activates Ca ATPase	Increased ATP consumption
Uncouple oxidative phosphorylation	Decrease ATP production
Increases neurotransmitter release	Activates glutamate receptor
Activates nitric oxide (NO) synthase	Increased NO–toxic

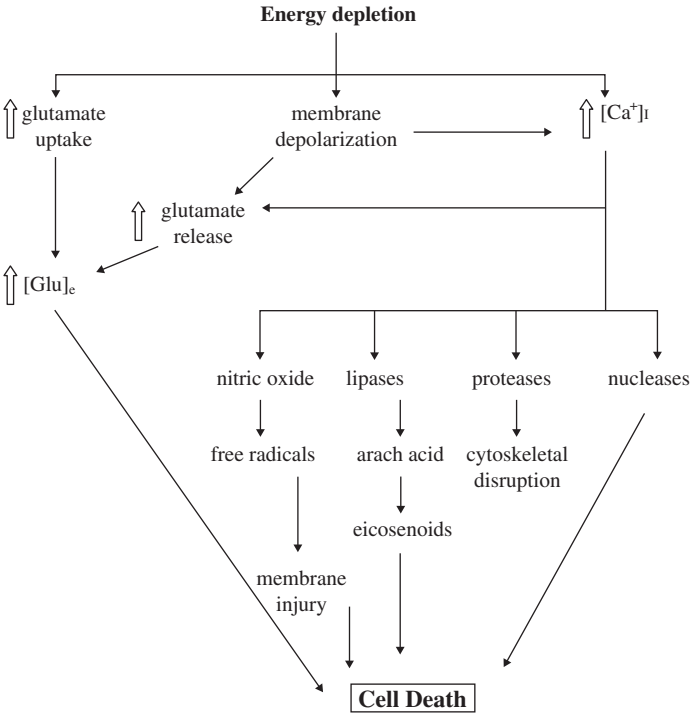


Figure 27.1. Pathophysiologic changes leading to neuronal cellular death following asphyxia.

may be seen anytime during the first week of life. The time of onset has been used to categorize the condition as either category 1 or 2. Category 1 foals are normal at birth with an onset of clinical signs 6–24 h later, while category 2 foals are clinically abnormal from birth. In category 1 foals, the onset of clinical abnormalities is usually abrupt and typically begins with altered consciousness expressed as loss of affinity for the dam, wandering, and loss of suckling ability. These signs may or may not progress to circling, blindness, abnormal phonations (hence the term "barker"), and seizures, which may be either generalized are partial. Partial seizures include "chewing gum" fits, lip smacking, or nystagmus. Affected foals often become recumbent and semicomatose. Other signs which are occasionally seen include abnormal respiratory patterns, mydriatic pupils, or dysphagia. Spinal cord signs, such as weakness or loss of specific limb reflexes, can also rarely be seen.[15]

Diagnosis of HIE is made based upon the presence of clinical signs and history which are consistent with the syndrome, as well as the exclusion of other illnesses with which it may be complicated, such as sepsis, meningitis, white muscle disease, prematurity, or Tyzzer's disease.

The "lavender foal syndrome" must be differentiated from HIE. The lavender foal syndrome, also known as coat color dilution lethal (CCDL), is a tetanic syndrome of Arabian foals of Egyptian breeding. Foals with this syndrome have a characteristic diluted coat color which varies from a striking silver to a pale lavender, pink, or pewter.[16] The syndrome is poorly described in the literature but has been recognized among Arabian horse breeders. Tetanic paddling with opisthotonus are present immediately after birth, interspersed with periods of relative normalcy. Routine clinicopathologic evaluation is normal but may be complicated by failure of passive transfer. Postmortem of the few reported cases does not reveal any changes of the CNS. Treatment success has not been reported in the literature, and affected foals have all been euthanized. The etiology of the syndrome is unknown. Diagnosis is by observation, breeding history, and rule-out of other similar conditions.

Due to the association with perinatal asphyxia, clinical signs of other body systems may be present

and complicate the diagnosis. Severe illness from other diseases may lead to signs of weakness and mental depression that are difficult to distinguish from HIE. Therefore, a careful physical and clinicopathologic examination is necessary to identify all potential abnormalities.

As HIE is by definition a noninfectious illness, the hemogram and blood chemistry panels are usually normal or reflect nonspecific stress or dehydration. Hypoxia and acidosis may be present due to concurrent respiratory disease or secondary to seizure activity. Cerebrospinal fluid (CSF) analysis is often normal but may show xanthochromia in excess of that seen in normal foals.[17] Mild xanthochromia is normal, and its presence neither supports nor refutes the diagnosis of HIE. CSF total protein and creatine kinase activity are normal.[18] Magnetic resonance imaging (MRI) or computerised tomography (CT) scanning of the brain is not readily available but has been attempted in some cases and may prove to be a useful adjunctive modality.

Pathologic examination may find concurrent signs of hypoxia, recumbency or sepsis. Examination of the CNS will often find signs of cerebral edema, hemorrhage, or cerebral necrosis.[8, 19]

TREATMENT AND PROGNOSIS

Treatment of foals with HIE must address the multisystemic nature of this disease. High quality nursing care is imperative and must include monitoring of blood gases, cardiac function, renal function, and nutritional status.

Correction of hypoxia (if present) is usually achieved by administration of oxygen by nasal insufflation (10 L/min humidified). Maintaining the foal in sternal recumbency is important to optimize the effects of supplemental oxygen therapy. If atelectasis, sepsis, or meconium aspiration is present, the response to oxygen will be incomplete. If respiratory depression due to CNS lesions is present, treatment may include theophylline 5–6 mg/kg intravenously followed by 1–2 mg/kg q12h.[20] The therapeutic range for theophylline is narrow, and caution should be exercised not to overdose. Toxicity results in seizures, tachyarrhythmia, and hypotension. Blood concentrations of theophylline should be monitored and the dosage adjusted to maintain therapeutic plasma levels of 5–20 mg/l.[20] If hypercarbia ($PaCO_2$ 60 mm Hg) and hypoxemia ($PaO_2 < 50$ mm Hg) persist, mechanical ventilation is necessary.

Appropriate fluid therapy is also important in foals with HIE and perinatal asphyxia. Polyionic isotonic replacement fluids should be given to correct dehydration and expand fluid volume. Overhydration should be avoided due to the failure of cerebral autoregulation and potential to exacerbate cerebral hemorrhage/edema. Metabolic acidosis should be treated with supplemental sodium bicarbonate, based upon the results of blood gas analysis. Alternatively, 1–2 meq of sodium bicarbonate (Na_2CO_3) is probably a safe empiric dose if blood gas data are not available. The clinician should be cautious, however, in the use of bicarbonate in a foal with severe respiratory compromise. In these foals, supplemental sodium bicarbonate can result in worsening of the acidosis, due to CO_2 retention. Specific electrolyte abnormalities should be corrected, as needed, and care should be taken to avoid administration of hyperosmolar fluids. Bolus dosing with hypertonic saline should probably be avoided in foals with HIE due to the risk of exacerbating neurologic damage due to abrupt osmolar shifts.

Seizures are an emergency situation and must be addressed immediately as the seizure potentiates CNS damage due to excessive depolarization and neurotransmitter release. Furthermore, seizures have profound effects upon blood pressure and CBF, further potentiating neuronal cell death. Diazepam (0.11–0.44 mg/kg IV) is the drug of choice. If more than three doses are required to control seizure activity, phenobarbital (2–10 mg/kg slow IV q 12 h) should be given. Phenobarbital should be maintained for 3–5 days, after which the dose should be incrementally decreased over at least 2 days. Abrupt withdrawal of phenobarbital can lead to recurrence of seizures. Control of seizures is further discussed in Section 2 Chapter 6.

Dimethylsulfoxide (DMSO) (0.5 g/kg IV as a 10% solution) has been advocated to treat cerebral edema, which was identified in 50% of foals in 1 report.[19] Increased CSF pressure has been recognized only rarely in the author's experience; however, it does occur and caudal herniation of the brain has been reported in foals.[21] DMSO also has anti-inflammatory properties, which may be beneficial in convulsing neonates. Mannitol has also been used to treat cerebral edema; however, its use in foals has

been limited due to concerns about its potential to exacerbate intracranial hemorrhage. This is probably overly cautious, and mannitol can be used in foals with HIE that do not show gross evidence of hemorrhage on spinal tap. Antioxidant drugs such as ascorbic acid and Vitamin E have been advocated; however, their penetration of the CNS is questionable, and they may have little value when given after the insult. Neither has been critically evaluated in neonatal foals.

Intravenous magnesium has been advocated for the treatment of HIE in foals.[22] Magnesium blocks Ca entry into the cell, while diminishing glutamate release.[23,24] Conflicting results have been published, however, regarding the efficacy of magnesium in hypoxic injury. As with other agents, the age of the subject and the timing of treatment appear to provide vastly different results. In a model of hypoxia in newborn rats, magnesium treatment was associated with recovery.[25] In another study, however, postasphyxial treatment worsened brain damage in 7-day-old rats.[26] Only limited studies have been reported in humans, and a clear benefit of the use of magnesium for HIE has not been established. Notwithstanding the conflicting results observed, doses of magnesium sulfate of 50 mg/kg/h for 1 h, then decreased to 25 mg/kg/h have been advocated with anecdotal success.[22]

Additional ancillary treatments include nutritional support, sepsis and gastric ulceration prophylaxis, and correction of failure of passive transfer (if present). Good nursing care with careful attention paid to keeping the foal clean and dry, minimizing decubitus formation, and maintaining intravenous and urinary catheters are critical to successful treatment.

In the author's experience, most foals have a minimum of 3 days during which the worst of the clinical signs are present, followed by gradual return to normalcy over the subsequent 5–7 days. Recovery from HIE occurs in somewhat the reverse order of its progression with return of consciousness, ability to stand, vision, and return of suckling ability usually the last to return. The occasional foal will have prolonged recovery, and lack of nursing ability has been occasionally observed up to 30 days after the illness. Recurrence is rare but can occur.

Most foals (85%) with uncomplicated HIE will survive, assuming appropriate treatment. Foals in category 1 are considered to have a better prognosis than foals in category 2.[27] In the author's experience, most foals which survive HIE usually have normal growth patterns and appear to perform equal to cohorts as they are put into work. Foals with complications such as sepsis, infected joints, or severe respiratory disease have a much lower survival rate that is dictated, in large part, by the nature of the complicating condition. Foals which demonstrate signs of cerebral necrosis (e.g., high protein, increased cellularity, and RBCs) on the spinal fluid examination, or which have refractory convulsions, have a poor prognosis.

REFERENCES

1. Drummond W, Koterba A. 1990. Neonatal asphyxia. In *Equine Clinical Neonatology*, edited by Koterba A, Drummond W, Kosch P, 124–35. Philadelphia: Lea and Febinger.
2. Giles RC, Donahue JM, Hong CB, *et al.* 1994. Causes of abortion, stillbirth and perinatal death in horses: 3,527 cases (1986–1991). *J Amer Vet Med Assoc* 203:1170–5.
3. Mayhew IG. 1989. Disorders of behavior and personality. In *Large Animal Neurology*, edited by Mayhew IG, 73–112. Philadelphia: Lea and Febinger.
4. Cohen ND. 1994. Causes of and farm management factors associated with disease and death in foals. *J Am Vet Med Assoc* 204:1644–51.
5. Rossdale PD, Mahaffey LW. 1958. Parturition in the thoroughbred mare with particular reference to blood deprivation in the newborn. *Vet Rec* 70: 142–52.
6. Doarn RT, Threlfall WR, Kline R. 1987. Umbilical blood flow and the effects of premature severance in the neonatal foal. *Theriogenology* 28:789–800.
7. Johnson P, Rossdale PD. 1975. Preliminary observations on cranial cardiovascular changes during asphyxia in the newborn foal. *J Reprod Fert Supp* 23:695–9.
8. Palmer AC, Leadon DP, Rossdale PD, *et al.* 1984. Intracranial haemorrhage in pre-viable, premature and full term foals. *Equine Vet J* 16:383–9.
9. Valla WE. 1986. Diagnosis and Treatment of Prematurity and Neonatal Maladjustment Syndrome in Newborn Foals. *Comp Cont Educ Pract Vet* 8:S211–23.
10. Volpe J. 1995. Hypoxic-ischemic encephalopathy: biochemical and physiological aspects. In *Neurology of the Newborn*, edited by Volpe J, 211–59. Philadelphia: W.B. Saunders.
11. LeBlanc MH, Huang M, Vig V. 1993. Glucose affects the severity of hypoxic-ischemic brain injury in newborn pigs. *Stroke* 24:1055–62.

12. Hattori H, Wasterlaein CG. 1990. Posthypoxic glucose supplementation reduces hypoxic-ischemic brain damage in the neonatal rat. *Ann Neurol* 28: 122–8.
13. Sheldon RA, Partridge JC, Ferriero DM. 1992. Postischemic hyperglycemia is not protective to the neonatal rat brain. *Pediatr Res* 32:489–93.
14. Westbrock GL. 1993. Glutamate receptors and excitotoxicity. In *Molecular and cellular approaches to the treatment of neurological disease*, edited by Waxman SG, 129–45 New York: Raven Press.
15. Mayhew IG. 1982. Observations on vascular accidents in the central nervous system of neonatal foals. *J Reprod Fert Supp* 32:569–75.
16. Fanelli HH. 2005. Coat colour dilution lethal ("lavender foal syndrome"): a tetany syndrome of Arabian foals. *Equine Vet Ed* 17:260–3.
17. Furr M, Bender H. 1994. Cerebrospinal fluid variables in clinically normal foals from birth to 42 days of age. *Am J Vet Res* 55:781–4.
18. Rossdale PD, Falk M, Jeffcoat LB, *et al.* 1979. A preliminary investigation of cerebrospinal fluid in the newborn as an aid to the study of cerebral damage. *J Reprod Fert Supp* 27:593–9.
19. Palmer AC, Rossdale PD. 1975. Neuropathology of the convulsive foal syndrome. *J Reprod Fert Supp* 23:691–4.
20. Koterba A. 1990. Appendix A. In *Equine Clinical Neonatalogy*, edited by Koterba A, Drummond W, Kosch P, 781–9. Philadelphia: Lea and Febinger.
21. Kortz GD, Madigan JE, Lakritz J, *et al.* 1992. Cerebral edema and cerebellar herniation in four equine neonates. *Equine Vet J* 24:63–6.
22. Wilkins P. 2001. Magnesium infusion in hypoxic ischemic encephalopathy. *Proc 19th Annual Amer College Vet Intern Med*, 242–3.
23. Berger R, Garnier Y, Jensen A. 2002. Perinatal brain damage: underlying mechanisms and neuroprotective strategies. *J Soc Gynecol Investig* 9: 319–28.
24. Leonard SE, Kirby R. 2002. The role of glutamate, calcium and magnesium in secondary brain injury. *J Vet Emerg Crit Care* 12:17–32.
25. Seimkowicz E. 1997. Magnesium sulfate dramatically improves immediate recovery of rats from hypoxia. *Resuscitation* 35:53–9.
26. Sameshima H, Ota A, Ikenoue T. 1999. Pretreatment with magnesium sulfate protects against hypoxic-ischemic brain injury but post-asphyxial treatment worsens brain injury in 7 day old rats. *Am J Obstet Gynecol* 180:725–30.
27. Hess-Dudan F, Rossdale PD. 1996. Neonatal maladjustment syndrome and other neurological signs in the newborn foal. *Equine Vet Ed* 8:24–32.

28
Miscellaneous Movement Disorders

Caroline Hahn

Medical neurologists define movement disorders "as neurological conditions that affect the speed, fluency, quality, and ease of movement." In this context, abnormal fluency or speed of movement (dyskinesia) may involve excessive or involuntary movement (hyperkinesia) or slowed or absent voluntary movement (hypokinesia). In humans, lesions in areas of the extrapyramidal upper motor neuronal system, particularly in the basal nuclei, commonly cause intermittent disorders of movement, but this has only rarely been recognized in animals. In horses, these are classified as conditions that result in altered muscle tone and movement, which of course includes ataxia, that is, deficits in general or special proprioception (most often due to spinal cord, cerebellar, or vestibular deficits) and generalized changes in muscle tone such as caused by tetanus, tremorgenic mycotoxins, and hyperkalemic periodic paralysis (covered in detail elsewhere). This chapter will focus on the most common examples of an enigmatic group of idiopathic disorders causing changes in gait and which do not, for the most part, relate to a focal central nervous system (CNS) lesion and thus do not include weakness and ataxia. These syndromes result from changes in the amount of resting muscle tone and the onset and force of muscle contraction due to a morphologic or, more probably, functional lesion. For the most part, no morbid or biochemical lesions are known, or if lesions have been identified, it is unclear how they result in the resulting movement disorders.

On occasion, horses may present for intermittent muscle spasms of a single limb. Some of these clinical signs then disappear and others remain constant. Partial damage to peripheral nerves or muscles or mild localized spinal cord disease are usually considered as causes but are mostly not proven. It is also worth remembering that horses with signs of spinal cord disease can have prominent hypermetria in one or both hindlimbs with hyperflexion, thus mimicking stringhalt, and a complete neurological examination should be performed on all cases of movement disorders that do not appear to have a classic orthopedic explanation.

In the final analysis, these disorders are due to an imbalance between muscle contraction and muscle relaxation that is regulated through the neuromuscular spindle, Golgi tendon organ, and myotatic reflex arc. Muscle stretch is regulated locally by muscle spindles (innervated by gamma motorneurons) whose afferent axons (1a fibers) synapse with lower motor neurons (a-motor neurons) and interneurons (classically 1a inhibitory interneurons). The reflex is important for the automatic maintenance of posture and muscle tone. Alpha and gamma motor neurons are regulated by higher control through upper motor neurons and a carefully controlled neurotransmitter balance (Figure 28.1).

In addition to this classic view of functional neuroanatomy, it is now known that an autonomous network of interneurons capable of generating a locomotor pattern exists independently of supraspinal inputs. This central pattern generator (CPG) is capable of activating motorneurons in an appropriate sequence as well as setting the excitability of other types of interneurons involved in transmitting information from descending pathways and sensory afferents, so that corrections through these pathways are commensurate with the various phases of the locomotor cycle.[1] It is now evident that a

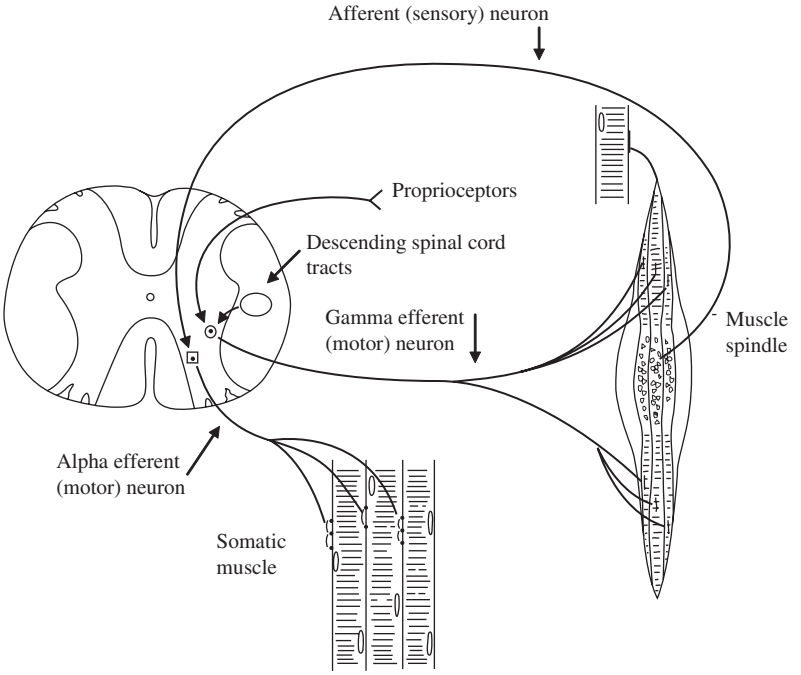


Figure 28.1. Schematic of the mechanism for the maintenance of muscle tone. When a muscle is stretched a volley of action potentials is triggered in muscle spindle 1a and II afferent axons. These axons activate excitatory synapses on alpha motor neurons in the ventral horn resulting in contraction of the muscle that was stretched. In addition, alpha motor neurons to antagonistic muscles are inhibited via interneurons. The sensitivity of this myotatic reflex is set by gamma motor neurons in the ventral horn that innervate the intrafusal fibers in the muscle spindle. Gamma motor neuron excitability in turn is controlled by descending upper motor neuron tracts from the brainstem. Damage to the descending spinal cord tracts leads to "disinhibition" of the gamma efferent neuron and an increased muscle tonus, expressed clinically as spasticity.

segmental organization of the locomotor-generating mechanisms exists whereby rostral and caudal segments may play different roles. In humans, there is some evidence to suggest the involvement of CNS pacemaker neurons, and the inappropriate release of CPG motor program may be the basis for several clinical disorders of movement.

EQUINE REFLEX HYPERTONIA

They have all new legs, and lame ones;
one would take it,
That never saw 'em pace before the spavin
Or springhalt regn'd among 'em.
—Shakespeare, Henry VIII, Act 1, Scene 3

Stringhalt ("Springhalt") is characterized by a sudden, apparently involuntary, exaggerated flexion of one or both hindlimbs during attempted movement. Varying degrees of hyperflexion with delayed protraction can occur, ranging from mild, spasmodic lifting, and grounding of the foot when the horse is backed or stopped suddenly to extreme cases during which the foot can contact the abdomen, thorax, and occasionally the elbow leading to a peculiar bunny hopping gait (Figure 28.2). Abnormal peripherally or centrally mediated reflex hypertonia and hyperereflexia affects particularly the lateral digital extensor muscle, but due to the action of the reciprocal apparatus, the whole pelvic limb is involved. Variations in the clinical signs with a lack of forced toe extension and abduction or caudal thrust of the limb at the onset



Figure 28.2. Horse with stringhalt showing involuntary hyperflexion of a pelvic limb.

of protraction may well indicate involvement of other muscles in the disease process. Bilateral pelvic limb or additional thoracic limb involvement—usually presenting as extensor hypertonus—is likely to indicate generalized neural involvement such as due to a neurotoxin. In horses with the classical signs of stringhalt, two distinct syndromes are recognized, plant-associated and sporadic stringhalt.

Plant-Associated Stringhalt

Plant-associated, or "Australian," stringhalt is a syndrome most often recognized in Australia[2,3] but has also been reported in New Zealand,[4] North America,[5,6] Chile,[7] and Japan[8] and is likely to occur infrequently in other countries. Usually many cases are seen in the one herd, and outbreaks have been associated with the ingestion of the related plants dandelion *(Taraxacum officinal)*, flat weed *(Hypochoeris radicata)*, and cheese weed *(Malva parviflora)*. The active agent, however, has not been isolated, and the same plant is common the world over. In Australia, cases tend to appear in late summer and are often associated with drier that normal summers. Older, taller horses are predisposed,[9] and cases are often more severe than seen in classical stringhalt and can progress to debilitating bilateral pelvic limb hyperflexion with delayed protraction during movement. Thoracic limbs can be involved and present as intermittent thoracic limb hypertonia with stumbling. Depending on the chronicity of the disease, there is marked atrophy of the distal limb musculature. Thoracolaryngeal responses are reduced early in disease progression. Most animals recover in a few days to up to 18 months (average 6–12 months) when removed from the affected pasture. Mephenesin,[2] baclofen,[10] and particularly phenytoin[11] have been reported to decrease the severity of clinical signs.

Changes on postmortem examination are consistent with those of a distal axonopathy preferentially affecting large axons with a decreased density of myelinated fibers and increases in endoneurial collagen and Büngner's bands (markers of repeated myelination and demyelination). Lesions are likely to be found as most somatic nerves and are most severe in the longest nerve, the recurrent laryngeal nerve. Muscles innervated by affected nerves show degrees of myopathic changes with large group atrophy, small angular fibers, internal nuclei, fatty replacement, dissecting fibrosis, and hypertrophy of intact fibers. Convincing central changes have not been reported. The reason for the extraordinary finding that peripheral nerve lesions in these cases result in hyperflexion, rather than the expected paresis with hypometria, has not been explained but is likely to involve specific changes in the fibers innervating the muscle spindles of particularly the lateral digital extensor muscles.

Sporadic Stringhalt

The sporadic form occurs worldwide and usually only affects one pelvic limb. The onset can be preceded by trauma to the dorsal tarsal region or the dorsoproximal metatarsus some weeks previously.[12] Etiologies are speculated to include tendon adhesions enhancing tarsocrural joint flexion or abnormalities in the myotatic reflex caused by tendon injury (specifically Golgi tendon organ injuries).

Surgical removal of a section of the myotendinous region, containing the Golgi tendon organs, of the lateral digital extensor muscle relieves the syndrome quite spectacularly in many cases.[12,13] Interestingly, the gait of some horses does not improve for several days after the surgery, suggesting that the change in gait is not just due to a mechanical effect. Before embarking on surgery, clinicians are urged to carefully examine the affected limb using ultrasonography, radiographs, and scintigraphy as appropriate,

to rule out and treat any underlying orthopaedic lesions. Asymmetric changes have been detected in the digital extensor muscles in some cases. In addition, it is worth remembering that in a retrospective study[12] of ten sporadic stringhalt cases, there appeared to be no real difference in the follow-up outcomes between four conservatively treated cases and six treated by extensive myotenectomy.

There has been no systematic survey of *post-mortem* lesions in sporadic stringhalt cases, but some severely affected animals have had extensive examinations with no evidence of histologic lesions in the CNS or motor unit (A. de Lahunta, personal communication). Interestingly, electromyography has shown abnormal activity while standing[14] and even spontaneous activity under anaesthesia (personal observation), the absence of neurogenic changes in an affected lateral digital extensor muscle having been confirmed in the latter.



Figure 28.3. Horse with Scandinavian knuckling syndrome showing paresis in the distribution of the peroneal nerve.

SCANDINAVIAN KNUCKLING HORSES

A neurological disorder characterized as "Scandinavian knuckling horse syndrome" with pathological lesions strikingly similar to plant-associated stringhalt has been documented in Scandinavia for the last decade.[15,16] At the time of publication, more than 140 horses are known to have been affected in Norway, Sweden, and lately also Finland, but very little has been formally reported. Cases occur during late winter or early spring when horses have been fed with silage preserved in plastic, although not all horses fed the same feed are affected on a premise. More than 50% of animals on individual properties can show clinical signs. Horses have shown varying degrees of usually symmetric knuckling of the metatarsophalangeal joints with stumbling and ataxia (Figure 28.3). In some animals, the clinical signs have worsened within some days until horses are unable to rise even when assisted, and mortalities of between 50 and 100% have been recorded. Cases with milder clinical signs have slowly recovered after convalescence period of 5–6 months (S. Hanche-Olsen, personal communication). A similar syndrome showing nerve and muscle lesions may be present in Japan.[17,18]

In one well-documented outbreak on a property in Finland, eleven of seventeen horses showed clinical signs that was progressive in seven horses and resulted in euthanasia. The only common feed was fresh ryegrass hay cut from a recently resown field. Horses developed clinical signs of fetlock knuckling due to poor digital extension of the metatarsophalangeal joints and paresis of the pelvic limbs ("dropping of the pelvis"). In the worst cases, clinical signs progressed within 3–4 weeks to severe paresis of the pelvic limbs, with animals "dog-sitting" and being unable to rise. The thoracic limbs appeared to be unaffected. On re-examination, 3 months after the onset of clinical signs, the horses showed paresis in the distribution of the peroneal nerve, accentuated by exercise. Careful neurological examinations did not reveal any proprioceptive deficits, overt hypometria, anesthesia of the peroneal nerve autonomous zone, or muscle atrophy in most of these animals, but one subsequently euthanized case showed prominent ataxia with conscious proprioceptive deficits in both the pelvic and the thoracic limbs. Lesions on post-mortem examination were limited to the peripheral nerves and muscle. Changes in the muscle were compatible with neurogenic atrophy, and detailed examination of the peroneal and radial nerves showed an evenly distributed, chronic-active, predominantly demyelinating polyneuropathy. Electron microscopy showed spectacular filamentous rough endoplasmic reticulum Schwann cell inclusions pointing toward abnormal posttranslational protein processing.

The putative toxin in this disease remains elusive, and despite the fact that the profound axonopathy somehow presents as hyperflexion rather than paresis, it is interesting to speculate whether a similar pathogenesis might be involved in the "knuckling" horses but principally targeting the peroneal nerve rather than the tibial nerve as in stringhalt. The ataxia observed in some of theses cases indicates that proprioceptive axons are also affected. Systematic work detailing the distribution of lesions and a thorough epidemiological investigation is now needed to try and identify the cause of this enigmatic disease.

SHIVERING (SHIVERS)

A further manifestation of a reflex hypertonia but affecting particularly the flexor muscles of the pelvic limbs is a syndrome referred to as shivering (shivers). The etiology is unknown but again is likely to involve an alteration in the feedback loop between 1a-afferent and gamma-efferent fibers. Other diseases that include shivering as their clinical signs include equine polysaccharide storage myopathy (EPSSM) and "stiff-horse syndrome." Compared with stringhalt cases, the pelvic limbs of shivering horses are flexed, abducted, and held in a spastic state for some time instead of being immediately returned to the ground as in stringhalt.

Classical shivering particularly affects draft breeds[19] and is characterized by involuntary flexion of the pelvic limbs and testicles as well as extension of the tail. Clinical signs are usually noticed when an attempt is made to back or turn the affected horse and may be accentuated by stress or excitement. The pelvic limbs are held off the ground in a flexed and abducted manner while muscles of the upper limb and tail may quiver. After a short time, the quivering ceases and the affected limb and tail return to a normal position. The horse then appears to be normal, but clinical signs reappear if attempts are made to turn or back the affected horse. In the early stages, owners often notice that the horse snatches up the hindlimbs when they are being picked up to clean the feet or to be shod. Classically, the condition is slowly progressive, but there is no way of predicting if or when they will deteriorate.

Even in well-developed shivering cases, signs may not be seen when the horse is standing still. In advanced disease, the affected animal may be unable to move backward more than a few paces, and sometimes, this cannot be performed at all. In some horses, there is evidence of involvement of the muscles of the thoracic limbs, neck, or even trunk and face, but it is unclear whether these present severe cases of classical shivering or represent other myotonic syndromes (such as "stiff-horse syndrome"). The difficulties backing into traces made this a disease of significant morbidity when draft horses were historically used. A hereditary predisposition is suspected.

Reflex hypertonia could potentially be caused by lesions in the sensory or motor pathways anywhere from the brainstem to the affected muscles and associated joint and tendon sensory receptors. Only rarely, however, specific lesions, such as focal spinal cord lesions, have been identified.[20] Some cases do have histologic evidence consistent with EPSSM,[21] and it was hypothesized that horses with shivers might have less stored glycogen and thus deplete their stores more rapidly, leading to localized muscle cramping. Other work, however, was unable to determine a significant association between EPSSM and shivering.[22] In addition to shivering, EPSSM cases should show other clinical signs including generalized weakness, mild to moderately increased serum creatine kinase, and abnormal polysaccharide accumulations in particularly type II muscle fibers.[23] In the author's experience in the United Kingdom, many shivering draft horses do not have increased muscle fiber polysaccharides but can have prominent myopathic changes (increased fiber size variation with centrally located, euchromatic nuclei), which suggest that some unknown myopathic process is occurring. It is possible that neurotransmitter defects occur to account for some of these baffling syndromes.

There is currently no effective treatment for this syndrome, and even though signs may improve after long periods of rest, the condition returns when work is resumed. It has been suggested that dietary treatment of affected draft horses with a high fat, low carbohydrate feed and a gradually increasing daily exercise program may be beneficial if instituted early in the course of the disease.[24] However, it seems unlikely that a dietary change would benefit cases of classic shivering without EPSSM.

STIFF-HORSE SYNDROME

Stiff-man syndrome (recently renamed as the more politically correct "stiff-person syndrome") is a rare

neurological disorder in humans characterized by continuous contraction of agonist and antagonist muscles, sometimes accompanied by involuntary sudden muscle spasms caused by involuntary motor-unit firing at rest. Variants of the syndrome may involve one limb only (stiff-leg syndrome). The disease is thought to be caused by immunological changes leading to a gamma-aminobutyric acid (GABA) transmission disturbance with antibodies produced against the enzyme glutamic acid decarboxylase (GAD), which is responsible for converting GABA into its active form. The precise pathogenesis, however, is not clear, and autoantibodies against GAD are not found in all human patients.[25] GABA is an important inhibitory central neurotransmitter, and a reduction in GABA activity can lead to continuous contraction of both agonist and antagonist muscle groups resulting in spasms.

Recently, a similar syndrome has been seen in horses in Belgium[26] and was called "stiff-horse syndrome." Clinical signs appear to wax and wane and range from mild muscle stiffness to sudden and often prominent muscle contractions. Mild-to-moderate muscle stiffness may be the only initial clinical sign and can be blamed on exertional rhabdomyolysis. Muscle enzymes, however, stay within normal limits, and there is no apparent weakness or muscle atrophy. Signs appear to be progressive and typically are initiated if the animal is startled, although they may occur spontaneously during voluntary movement. The lumbar and pelvic limb muscles are typically involved with horses appearing to get "stuck" from a few seconds to many minutes during severe episodes. Between episodes, the horse may appear normal or generalized myotonia may be evident.

Cases are currently diagnosed by the exclusion of other diseases including tetanus, equine motor neuron disease, hyperkalemic periodic paralysis, unusual spinal cord disease, thoracolumbar discospondylosis, and longissimus myopathies. Physical examination is generally unremarkable, and a neurological examination will likely fail to detect any abnormalities apart from the intermittent hypertonia. Results of routine blood screening tends to be unremarkable, but it is important to eliminate rhabdomyolysis and electrolyte abnormalities from the differential diagnosis. A muscle biopsy of the semimembranosus or gluteal muscles should be performed to rule out exertional rhabdomyolysis and EPSSM.

The confirmatory diagnostic test is the detection of antibodies against GAD in serum and cerebrospinal fluid; however, several strongly suspected cases have been negative on this test. Administration of benzodiazepines at an initial dose of 0.05–0.1 mg/kg diazepam, administered by slow intravenous injection, should in theory reduce or alleviate the severity of the muscle spasms and can be used as a crude diagnostic test: pronounced paradoxical excitement on administration has, however, been observed.

In humans, drugs that enhance GABA neurotransmission, such as diazepam, vigabatrin, and baclofen, provide mild to modest relief of clinical symptoms. Owing to the scarcity of cases and difficulty in making a definitive diagnoses, no studies addressing treatment options in affected horses have been published. Steroid administration (prednisolone PO at 2 mg/kg/day) may be a potential medium to long-term treatment option in the horse. Complications such as laminitis at this dose are a realistic risk, but lower doses appear to have little effect (Joe Mayhew, personal communication).

Stiff-man syndrome in humans is a painful condition and is likely to be the same in horses. Nonsteroidal antiinflammatory drugs (NSAIDs) appear to have little effect in alleviating this apparent discomfort, and the long-term welfare of affected horses should be considered.

FIBROTIC MYOPATHY

Fibrotic myopathy is most commonly caused by scarring or an induced reflex hypertonia of the semitendinosus and sometimes the gracilis muscle. The pelvic limb foot is slapped to the ground at the end of the swing phase causing a shortening of cranial phase of the stride.[27] Classically, this is a nonpainful, chronic, progressive, idiopathic, degenerative disorder caused by mechanical scarring of these muscles, but some cases may be due to an induced reflex hypertonia in the semitendinosus muscle, and three cases of fibrotic myopathy due to a peripheral neuropathy have been described.[28] A very similar syndrome is recognized in dogs. Affected muscles are characterized by contracture and fibrosis, and normal tissues are replaced by dense collagenous connective tissue. Most cases are associated with lesions such as muscle tears and injection reactions

in the region of the caudal thigh muscles,[29] and diagnostic ultrasound is useful to define the nature and extent of the inciting lesion. Surgical release of affected tissues through tenotomy[30–32] produces inconsistent results. Prognosis is guarded due to recurrence.

REFERENCES

1. Rossignol S, Bouyer L, Barthelemy D, *et al*. 2002. Recovery of locomotion in the cat following spinal cord lesions. *Brain Res Brain Res Rev* 40:257–66.
2. Dixon RT, Stewart GA. 1969. Clinical and pharmacological observations in a case of equine stringhalt. *Aust Vet J* 45:127–30.
3. Huntington PJ, Jeffcott LB, Friend SC, *et al*. 1989. Australian stringhalt—epidemiological, clinical and neurological investigations. *Equine Vet J* 21: 266–73.
4. Cahill JI, Goulden BE, Pearce HG. 1985. A review and some observations on stringhalt. *N Z Vet J* 33: 101–4.
5. Galey FD, Hullinger PJ, McCaskill J. 1991. Outbreaks of stringhalt in northern California. *Vet Hum Toxicol* 33:176–7.
6. Gay CC, Fransen S, Richards J, *et al*. 1993. Hypochoeris-associated stringhalt in North America. *Equine Vet J* 25:456–7.
7. Araya O, Krause A, Solis de Ovando M. 1998. Outbreaks of stringhalt in southern Chile. *Vet Rec* 142:462–3.
8. Takahashi T, Kitamura M, Endo Y, *et al*. 2002. An outbreak of stringhalt resembling Australian stringhalt in Japan. *J Equine Sci* 13:93–100.
9. Slocombe RF, Huntington PJ, Friend SC, *et al*. 1992. Pathological aspects of Australian stringhalt. *Equine Vet J* 24:174–83.
10. Cahill JI, Goulden BE. 1992. Stringhalt—current thoughts on aetiology and pathogenesis. *Equine Vet J* 24:161–2.
11. Huntington PJ, Seneque S, Slocombe RF, *et al*. 1991. Use of phenytoin to treat horses with Australian stringhalt. *Aust Vet J* 68:221–4.
12. Crabill MR, Honnas CM, Taylor DS, *et al*. 1994. Stringhalt secondary to trauma to the dorsoproximal region of the metatarsus in horses: 10 cases (1986–1991). *J Am Vet Med Assoc* 205:867–9.
13. Torre F. 2005. Clinical diagnosis and results of surgical treatment of 13 cases of acquired bilateral stringhalt (1991–2003). *Equine Vet J* 37: 181–3.
14. Wijnberg ID, Back W, van der Kolk JH. 2000. [The use of electromyographic examination as a diagnostic tool and phenytoin sodium as treatment in a case of classic springhalt in a Dutch warmblood horse]. *Tijdschr Diergeneeskd* 125:743–7.
15. Gustafsson K, Roneus M. 2000. Utbrott av neurologisk störning med okänd etiologi hos hästar [Outbreak of neurological disease with unknown etiology in horses]. *Svensk Veterinärtidning* 52: 253–9.
16. Ihler CF, Hanche-Olsen S, Teige J. 2002. Extensor weakness due to peripheral neuropathy in horses with possible feed related aetiology. *Br Equine Vet Assoc* 203.
17. Furuoka H, Okamoto R, Kitayama S, *et al*. 1998. Idiopathic peripheral neuropathy in the horse with knuckling: muscle and nerve lesions in additional cases. *Acta Neuropathol (Berl)* 96:431–7.
18. Furuoka H, Mizushima M, Miyazawa K, *et al*. 1994. Idiopathic peripheral neuropathy in a horse with knuckling. *Acta Neuropathol (Berl)* 88: 389–93.
19. Mitchell WM. 1930. Some further observations on pathological changes found in horses affected with shivering and their significance. *Vet Rec* 10: 535–7.
20. Davies PC. 2000. Shivering in a thoroughbred mare. *Can Vet J* 41:128–9.
21. Valentine BA, Lahunta AD, Divers TJ, *et al*. 1999. Clinical and pathologic findings in two draft horses with progressive muscle atrophy, neuromuscular weakness, and abnormal gait characteristic of shivers syndrome. *J Am Vet Med Assoc* 215:1661–5.
22. Firshman AM, Baird JD, Valberg SJ. 2005. Prevalences and clinical signs of polysaccharide storage myopathy and shivers in Belgian draft horses. *J Am Vet Med Assoc* 227:1958–64.
23. Valentine BA. 2003. Equine polysaccharide storage myopathy. *Equine Vet Educ* 15:254–62.
24. Valentine BA, Van Saun RJ, Thompson KN, *et al*. 2001. Role of dietary carbohydrate and fat in horses with equine polysaccharide storage myopathy. *J Am Vet Med Assoc* 219:1537–44.
25. Levy LM, Dalakas MC, Floeter MK. 1999. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. *Ann Intern Med* 131:522–30.
26. Nollet H, Vanderstraeten G, Sustronck B, *et al*. 2000. Suspected case of stiff-horse syndrome. *Vet Rec* 146:282–4.
27. Adams OR. 1961. Fibrotic myopathy and ossifying myopathy in the hindlegs of horses. *J Am Vet Med Assoc* 139:1089–92.
28. Valentine BA, Rousselle SD, Sams AE, *et al*. 1994. Denervation atrophy in three horses with fibrotic myopathy. *J Am Vet Med Assoc* 205:332–6.

29. Turner AS, Trotter GW. 1984. Fibrotic myopathy in the horse. *J Am Vet Med Assoc* 184:335–8.
30. Bramlage LR, Reed SM, Embertson RM. 1985. Semitendinosus tenotomy for treatment of fibrotic myopathy in the horse. *J Am Vet Med Assoc* 186: 565–7.
31. Gomez-Villamandos R, Santisteban J, Ruiz I, *et al*. 1995. Tenotomy of the tibial insertion of the semitendinosus muscle of two horses with fibrotic myopathy. *Vet Rec* 136:67–8.
32. Adams SB, Fessler JF. 2000. *Atlas of Equine Surgery.* Philadelphia: PA Saunders.

29
Stereotypic and Other Behavior Problems

M. D. Marsden

There are a wide range of seemingly bizarre behavior patterns considered undesirable by horse owners for which they may seek veterinary advice and treatment. Owner concerns are often misplaced in some respects and they may have attempted traditional treatments that are ineffective, detrimental to the horses' welfare, or may exacerbate the problem. Conversely, aspects of these behavior patterns that should alert owners and veterinary surgeons to potentially serious clinical or welfare issues may be overlooked, delaying appropriate treatment and care.

These bizarre behavior patterns are often referred to by the colloquial term "stable-vice". The term vice however is inappropriate, implying that it is the horse which is at fault, although stable correctly emphasizes the environment in which these behavior patterns are generally seen. It was suggested as early as 1839[1] that such behavior patterns were *diseases of domestication* and it is now widely recognized that stable-vices are not *misbehavior* but, like similar behavior problems seen in other domestic livestock, are a sign of inappropriate husbandry.[2–6] The horse evolved as a highly social herd-living animal roaming arid, sparsely vegetated plains[7] surviving by increasing intake of highly fibrous material[8]; most horse husbandry systems differ greatly from this.[9] Although meeting most of the horse's physical needs, they may not meet all of their psychological or behavioral needs, and the resulting changes in behavior, including the development of stable-vices, are a welfare issue.[10]

Understanding which key features of husbandry practices are responsible for these behavior patterns in stabled horses, along with studies of genetic susceptibility, underlying neuropharmacology, and applied learning theory offers considerable scope for effective and appropriate treatment and prevention.

DIFFERENTIAL DIAGNOSES

Many different behavior patterns are collectively referred to as stable-vices, and careful observation is required in order to correctly assess and treat the presenting problem. Many of the behavior patterns described as stable-vices are stereotypes, classically defined by their repetitive nature and the lack of an obvious external goal or function. Included in this category are crib-biting, wind-sucking, weaving, box-walking, circling, pacing, head-twisting, tongue-flicking, tongue-curling, teeth-grinding, heel-tapping, rein-snatching, rug-tearing, and self-mutilation. Some, such as wood-chewing and coprophagia, are signs of specific dietary deficiencies, and others such as hay-dipping, door-banging, and stall-kicking are learned behavior problems. Pawing occurs for many different reasons in the horse. It can be part of a stereotypy but is most often a sign of acute frustration that can develop into a learned behavioral problem. Morbid cerebral pathology, congenital fourth branchial arch defects, infestations, primary skin disorders, dental problems, headshaking, and pathological aggression can all be presented to veterinarians as behavior problems or stable-vices by owners.

In order to facilitate diagnosis, particular attention should be paid to the nature, timing, precipitating factors, and consequences of the behavior. A full history of husbandry practices highlighting any recent changes especially in pasture, feeding, and social companions will also be particularly useful.

Clinical signs are not usually necessary to positively diagnose stereotypic behavior, but they can be

useful when dealing with post-sale disputes to distinguish newly acquired stereotypes from those which have been established for some time and as evidence as to whether or not the stereotypy occurred in a previous home.

For example, development of the ventral neck muscles, as well as that of the sternocephalicus and sternohyoideus, are typical of frequent crib-biting and some forms of wind-sucking. These are difficult to distinguish from changes due to some ridden work and some common ridden evasions, however. Patterns of wear are more useful, such as the upper incisor teeth in crib-biting or hair on the muzzle in some forms of wind-sucking. The front shoes are unevenly worn on the outside edges in a mirror image of each other in a horse which weaves. A corresponding pattern of wear should be found on the surface on which the horse weaves.

Wood-chewing and crib-biting are often confused in post-sale disputes, but can easily be distinguished by the different physical evidence left by each, and which can be particularly useful when the horse involved has been sold or destroyed. On fence posts, for example, wood which has been chewed splinters at the top of the teeth marks, due to upwards scraping from the lower incisors, resulting over time in fence posts appearing narrower, even sharpened at the top. By contrast, in crib-biting the wood is splintered off at the bottom of the teeth marks and after some time, the post appears flattened or hammered out at the top. Furthermore, the crib-biting horse tends to concentrate activity in one or two spots, whereas a horse that is wood-chewing will usually range over a wide area chewing a little off many fence posts or many different parts of the box.

A horse with a stereotypic pacing pattern developed consistent with the design of its original box will initially crash into the wall if placed in a new box where it is physically impossible to carry out the original routine. Horses which pace or box-walk may appear to step or trip over, move around, or sniff at non-existent objects, or stop and turn as if to look out where there is no window should appropriate objects and stimuli have been in that position in the box where the horse developed the stereotypy. Where box designs are sufficiently different, this can often be used to determine whether or not stereotypic pacing could have developed in the new box after a horse was sold or was more likely to have developed in the old box, prior to sale, depending on which box the fine details of the stereotypy best fits.

A few locomotory stereotypes such as circling, box-walking, and pacing are similar at first glance to signs of some neurological problems. In contrast to the compulsive circling seen in morbid cerebral diseases, the direction of stereotypic circling and box-walking can vary between bouts. The horse performing a stereotypy will remain responsive to environmental stimuli and routine handling procedures and shows no asymmetry in sensation or facial expression.

Horses with congenital fourth branchial arch defects (FOUR-BAD) are sometimes described as *wind-suckers* by owners. These horses are truly aerophagic, may be unthrifty, and are reported to be prone to tympanitic colic.[11] This condition can be distinguished from stereotypic wind-sucking by palpation and endoscopy; in horses with FOUR-BAD, the cricopharyngeus and cricothyroideus muscles are absent or hypoplastic.[12] These structures are normal in horses with stereotypic wind-sucking, which do not actually swallow air but take it into the distal esophagus and burp it back out again to make the characteristic noise that most owners find irritating.

Apart from the obvious lack of any evidence of infestation other than these behavior patterns, the most useful distinguishing feature in horses with self-mutilation is the pattern of lesions. Horses with stereotypic self mutilation tend to bite and lick the chest, flank, and particularly in stallions, the inside of the forearm and area behind the knee, and rugs if worn are torn in these places.

Box-walking is often first presented as a suspected dental problem, the owner mistaking feed scattered around the box for quidding. Crib-biters may also be presented as suspected dental or worming problems with unexplainable weight loss once the upper incisors become sufficiently worn to inhibit grazing. Primary dental problems leading to learned ridden evasions are often also associated with bridling problems and can be distinguished from other learned ridden evasions by the suddenness of the horse's response to the rider's contact at certain times when riding seen in association with other indicators of pain including tucked lower lip, hollowing of the back, tucking of the tail, and upwards motion of the head and neck with the muzzle thrown out and up. Horses which deliberately pull on the rider or have learned to throw their head to distract the rider do this by pulling forwards initially and then leaning a bit before further head movements.

Agoraphobia and claustrophobia have never been diagnosed in horses, but such anthropocentric terms are sometimes used to describe pacing along a fence line or box-walking. They are also often used to describe learned behavior problems where horses become agitated when in the field (agoraphobia) or stable (claustrophobia) and jump out. This is usually caused by inappropriate social grouping or feeding, and careful attention to husbandry changes associated with the onset of the problem is usually enlightening as to the exact cause and thereby the necessary husbandry changes required to resolve the problem.

Some wind-suckers develop a bald patch that may become a chronic lesion on the lower lip, muzzle, or chin should they use a vertical surface. Some forms of stereotypic feed-related pawing can result in painful contusions. Idiopathic lesions on dorsal aspects of the hocks of a mare with a foal at foot may be due to the foal cribbing on its mother's hocks.

It is important to make a distinction between pathological headshaking, stereotypic headshaking, and learned evasions. In pathological headshaking, the initial movement of the muzzle is down and in. This movement is very sudden and may be relatively tiny. Immediately thereafter, the head and muzzle may be thrown upwards to varying degrees, often primarily in a vertical plane. Video analysis can be helpful in evaluating such cases. The nature of the head movement is consistent but gradually worsens over time; this also occurs at pasture. In most learned ridden evasions, the problem behavior will vary with the rider and his/her actions and will have a clear trigger factor related to a specific element of the ridden exercise, the arena used, and/or the rider's actions. In stereotypic headshaking, the movement is strictly the same over time and does not vary with exercise, work, or the rider's actions. The movements in these latter two types of headshaking can be in any plane with various degrees of rotation.

Aggression may be learned or pathological. A variety of hypothalamic-pituitary-adrenal (HPA) axis pathologies can cause aggressive behavior. In this case, the aggressive behavior is generalized i.e., toward all people, horses, and other animals. The behavior is usually proactive and is expressed as biting, foreleg striking, and chasing. This is similar to the aggression seen as a side effect of corticosteroid therapy in some individuals. Threats may not be seen at all or are brief and quickly followed by actual aggressive activity. In contrast, learned (non-pathological) aggression tends to be expressed differently toward specific people or horses and may be restricted only to particular individuals. Learned aggressive behavior can be either proactive biting and chasing or defensive kicking, and threats are common. With success over time, this kind of aggressive behavior becomes primarily threats or intention movements with relatively little actual biting, chasing, or kicking being required to initiate the desired reactions in others.

A positive diagnosis of learned misbehavior can be made when the following key diagnostic features are found. A clear trigger factor should be apparent, known as the antecedent for the problem behavior, and this behavior should be followed within half-a-second by a positive consequence from the horse's point of view. This can be remembered by the mnemonic ABC, describing the sequence antecedent-behavior-consequence. The development of the problem over time should follow the classic sigmoid learning curve, i.e., it should begin relatively slowly and then increase exponentially before rapidly steadying to the current level of frequency.

There are a number of key diagnostic features of all stereotypic behavior distinguishing this from learned behavior and other similar problems. The features can be grouped into the following categories (Table 29.1) remembered by the mnemonic GREAT:

- Goals
- Repetition
- Eating
- Arousal
- Threats

In learned behavior problems, there is always an external goal, although this may not be immediately obvious. For example, even a slight and transient reduction in pressure (reins, seat, legs, and others) or work constitutes a reward and is a common goal of many learned behavior problems. The goal of hay-dipping, for example, is a more succulent, softer mouthful, and this behavior can be extinguished over a two-week period along a learning curve by feeding hay already soaked for 30 min, thereby removing the goal as now dunking the hay in water has no further beneficial effect from the horse's point of view.

As bizarre as many stereotypes may appear, all are elements of *normal* behavior patterns that are

Table 29.1. Distinction Between Stereotypy and Other Behavior Problems

Nature of Behavior	Stereotypy	Learned Behavior	Dietary Deficiency
G—external ***Goal*** obvious	No	Yes	Yes
R—strictly ***Repetitive***	Yes	No	No
E—increased after ***Eating***	Yes	No	Yes
A—stimulated by ***Arousal***	Yes	No	No
T—stopped by ***Threat*** or actual punishment	No	Yes	No

attenuated or isolated from their usual external *goal* or *function*. Examples include teeth-grinding in the absence of food to be chewed or tongue flicking in the absence of grasses to be selected.

Stereotypic behavior is traditionally defined by a lack of an obvious external goal or function. However, it has been shown that performing stereotypic behavior in other species, including children with autism, calms the affected individual, and equivalent comparative biochemistry and physiology suggests that the same is likely to be true in the horse. Such a function would also explain the most outstanding definitive characteristic of stereotypic behavior—its repetitive nature—as strictly repetitive activities produce very predictable neural feedback which has a calming or *de-arousing effect* mediated by associated homeostasis of the various neurotransmitters and stress hormones involved. Hence for stereotypic behavior, it is the actual performance of the activity which is the goal or motivating factor.

This is the reason why it is so detrimental to welfare to physically prevent stereotypic behavior, using cribbing straps, for example. This is directly analogous to trying to deal with people with Obsessive Compulsive Disorders by physical restraint—ineffective and inhumane. In this author's opinion there is no such thing as a "humane" cribbing strap.

Stereotypic behavior is traditionally defined by a repetitive nature. The elements of many learned behavior problems often appear to be repetitive; however, close examination shows variation in the sequencing and duration of the different elements occurs. Stereotypic behavior is strictly repetitive with the number, sequence, and duration of every element remaining consistent, even to the extent of continuing to incorporate a step over an obstacle or a glance to a window when performing the stereotypy elsewhere than the place it originally developed and where there is no such obstacle or window, lending a bizarre aspect to the behavior shown.

Sudden arousal such as the crack of a whip, yell, or bang will interrupt the performance of a learned behavior problem. In contrast, such arousal will stimulate and exacerbate stereotypic performance.

Some stereotypic behaviors, such as crib-biting and box-walking, are directly stimulated by eating and continues intermittently with consumption-related biting and chewing, increasing in frequency once feeding finishes. Hay-dipping also is seen during eating but by contrast diminishes in frequency as feeding finishes. Wood-chewing and coprophagia do not interrupt feeding.

In contrast to learned behavior problems, stereotypic behavior is not stopped by threats or punishment. As the goal of the behavior is its actual performance, subsequent pain or adverse consequences do not affect it. This is the reason for the apparent paradox of stereotypes such as self-mutilation and some feed-related pawing where these activities maintain open wounds and foals continuing to crib-bite on the mare's hocks despite repeated injuries from her vigorous objections!

To date, there is no reported information on the effect of punishment on wood-chewing and coprophagia. As these are signs of dietary deficiency, it is unlikely that punishment or adverse consequences will affect their performance, and clients usually report the ineffectiveness of punishment as a deterrent here as one of their main concerns that this must mean something is wrong with their horse.

COMMON STEREOTYPIC BEHAVIORS

Any odd or unusual behavior characterized by a highly repetitive nature and the lack of an obvious external goal and that does not result from a morbid pathological process can be regarded as a stereotypy. Stereotypic activities, however bizarre they may initially appear, commonly contain isolated elements of normal feeding and locomotory behavior, and the more frequently a particular action occurs in the normal behavioral repertoire of the horse, the more likely it is to be seen as a stereotypy. Stereotypic behavior will be stimulated by arousal, for example, when the horse is disturbed, pleasurably excited, frustrated, anxious, fearful, or in pain, and many of these activities are seen while eating, particularly after a palatable treat. It is most commonly seen when anticipating feed, when leaving familiar horses or handlers, meeting new horses or handlers, on turn-out into a paddock or new box, when confined and isolated including for traveling, and common husbandry practices such as weaning, starting schooling, training, and changing routine can all precipitate stereotypy performance. When a horse is sold, many of these events occur together and it is possible for a horse that showed no signs of stereotypy in the previous environment but to show this immediately upon arrival in the new environment.

Although some stereotypes, such as self-mutilation for example, do result in deleterious physical consequences for the horse and for this reason may be brought to veterinary attention, many do not and owner concern is often misplaced in this respect. There are also, however, financial implications to the appearance of a stereotypy. For example, one survey of English thoroughbreds found the market value of a horse to fall by an average of 37% should it develop a stereotypy.[13] The exact amount depended on the nature of the stereotypy, with the greatest loss being for crib-biting and wind-sucking, resulting in a 50% fall in price, and the least loss being for rug-tearing, this approximating to the cost of rug repair. For most other stereotypes, however, this survey could find no real costs (e.g., in increased veterinary bills, feed costs, difficulty in training, or poorer performance) to explain the perceived drop in value and concluded that horses with stereotypes were a "bargain." This does however represent a serious concern for many, particularly professional owners.

Crib-biting

The crib-biting horse will take hold of a stable door, manger, ledge, fence post, or other solid projection, usually at approximately sternum height, using incisor teeth. Then, primarily by pressing down hard with the upper incisors, the horse will arch the head and neck in a characteristic fashion associated with contraction of the sternocephalicus and sternohyoideus muscles or extend the neck. It may further rock gently backwards, slightly flexing the hocks to bite or pull down and back on the surface used. Some horses will lick and mouth the surface briefly in their own particular way prior to biting the object. The frequency of biting varies both between horses and within individuals, commonly, for example, occurring in bouts of 2–3 bites every 10–20 seconds. Such episodes may be seen for a short time after a sudden disturbance, for some minutes after eating a palatable (sweet) treat or concentrate feed, and may continue at a reduced frequency for a few hours whilst eating hay or other forage. Horses that crib-bite while turned out may stop grazing and leave companions to go to a gate or fence post that is suitably solid and of a convenient height to pursue the activity. In some horses, crib-biting may increase or be seen only when the horse is in pain.

When carried out on metal or other hard surfaces, crib-biting can cause characteristic chipping and excessive wear of the incisor teeth. When using a wooden surface, splinters can cause minor oral lesions.

The surfaces used for crib-biting become worn and chipped, with multiple indents or scratches being obvious, especially on the top of the object involved. This environmental damage can be a cause of concern, but it is usually the wind-sucking that is frequently associated with crib-biting, and the fear that other horses will *copy* this *bad habit* is of primary concern to the owners (Figure 29.1).

Wind-sucking

Stereotypic wind-sucking occurs in similar situations to crib-biting, when disturbed and during or after eating, although there are few additional physical signs.

Wind-sucking is the colloquial term used to describe the proximal esophageal distention seen primarily during crib-biting, associated with a high proportion of the *bites* made. It is however also seen in some horses in an activity where the head and



Figure 29.1. A horse demonstrating the characteristic behavior of cribbing. Excessive wear on the incisor teeth is apparent.

neck are arched in a similar way as when crib-biting but without biting down on a surface. The horse may nod its head, bite gently on its lip, make sharp upwards or nodding movements of the muzzle, or flap the lips while flexing the head to various degrees toward the sternum just before the sternocephalicus and sternohyoideus muscles are contracted. Most of these horses emit a characteristic grunting sound within a second or so of this. Perhaps it was the gulping nature of this sound that helped create the myth that horses swallow air at this point.

Many owners cite this putative swallowing of air as their main concern and suspect this as a cause of colic and poor condition as they believe that their horse is "filling itself up with air." There is however no scientific evidence for this. Furthermore, combined endoscopic and fluoroscopic observations have shown that while a column of air does suddenly appear in the proximal esophagus during the wind-sucking associated with crib-biting, this is expelled through the cranial esophageal sphincter into the pharynx as the *grunt* is heard and that very few air boluses are passed toward the stomach.[11] Many "conditions of sale" describing wind-sucking as the habitual swallowing of air should therefore be amended in the light of this study and alternative diagnoses sought for any accompanying colic or unthriftiness.

Box-walking

In this syndrome, the horse will walk, jog, or trot around the perimeter of its box or enclosure, often at a brisk pace. Like crib-biting and wind-sucking, this also occurs usually after feeding or while eating hay and other forages. It is also more likely to be seen after extra physical exertion or when the horse may be anticipating such an event. The box-walking horse may routinely pause to look out of a door or window or to sniff the ground. Direction and speed may vary although intensity usually rises to a peak shortly after eating a concentrate feed or forage is given, declining gradually thereafter. This activity wears a path in the bedding and pieces of feed and forage may be scattered in a characteristic fashion, dropped as the horse snatches a bite and chews while moving around its box or yard. If the horse is moved, the size and shape of the path is likely to change to follow the perimeter of the new enclosure.

The owner may be concerned about weight loss or unthriftiness and may suspect tooth problems on noticing the dropped feed. Prolonged bouts of box-walking have been known to precipitate episodes of rhabdomyolysis in a susceptible horse, and this stereotypy may also occur as a short-term side effect of acupuncture treatment in the horse.

Weaving

A horse that weaves sways from side to side in a rhythmic manner, typically when looking out over the stable door. One or both forelimbs may be lifted off the ground as the head reaches its extreme point to the opposite side and in some cases one or two sideways steps may also be incorporated in the routine. The head usually is extended slightly and some horses may nod their head in mid-swing. The horse will remain alert and responsive to stimuli. Weaving typically occurs when the horse is anticipating the arrival of feed, and some horses may intersperse weaving with neighing and pawing at the door in a typical frustration response. In contrast to crib-biting, wind-sucking and box-walking, weaving usually stops once the horse is fed and is eating.

Weaving is also seen when the horse is disturbed or excited, particularly by the movement of other horses. It can be seen at pasture, typically at a gateway or along a fence line when the patient is left behind or is waiting to be brought in. Some horses will weave in a loose-box but not a tie-stall, even though there is plenty of room to perform the activity. If physically prevented from weaving, such as by closing the top part of the stable door or using an anti-weaving grille that tightly restricts the horse's neck

when it is looking out of the box, most horses will simply step back and continue the routine or change the pattern to accommodate the restriction by head-twisting only. With such restrictions in place, the frequency and intensity of weaving/head-twisting may increase with faster and more violent swinging.

Many owners consider weaving at feeding time normal and may only become concerned if shoes or hooves become unevenly worn or unusual neck muscle development is seen. Weaving has been blamed for tendon and ligament strain although there is no evidence for this, and it is extremely rare that the horse becomes violent enough to cause it to slip with consequent injury. A worn patch at the doorway (or fence line) may become noticeable over time.

Pacing

Pacing refers to repeated walking back and forth along a particular section of fence line or stable-wall in a predictable routine manner. Owner concerns are similar to those for box-walking and they may also describe the horse as anxious or panicky. The pacing routine can be complex, involving elements of other behavior patterns, such as head-turning, for example, as if to look at something, pawing, sniffing at the ground, and short pauses. Careful observation is required to distinguish this stereotypy from an acute frustration reaction after being unexpectedly hindered from escape by a boundary. To be accurately described as stereotypic, the pacing must have a high degree of redundancy by being performed in a strict routine, the sniffs, turns, and pauses always occurring at the same time at the same places. The horse may investigate, avoid or step over real and non-existent obstacles. It may also be responsive to novel stimuli and sniff or look at real objects introduced while pacing. A path may be worn in the ground or bedding. When turning at each end of the path, elements of this stereotypy may be very similar to weaving and it is usually seen in similar circumstances.

Pacing may also occur as a post-operative complication, after prolonged surgery, and the use of relatively large amounts of opioid-based analgesics such as morphine.

Circling

Circling describes the syndrome wherein a horse turns repeatedly to walk in small circles, often in a preferred direction. This is a relatively unusual stereotypy and may initially present as a suspected neurological problem. In contrast to compulsive circling in one direction seen with morbid cerebral diseases, the direction of stereotypic circling may vary. The path of the circle remains relatively constant for each horse irrespective of the boundary, distinguishing this from box-walking. Circling is commonly carried out in a corner or at a boundary, but not always. It is most often seen when an affected horse is initially released into a stable or paddock but is also seen when the horse is first disturbed or becomes excited. The horse may appear distracted from its environment but, as with other stereotypes, remains responsive to handling and to other routine stimuli.

Pawing

Stereotypic pawing is seen in many horses immediately after receiving a concentrate feed. Typically, the horse will wait for the feed to be given with one forelimb raised. Although both forelimbs may be used at different times, usually one is preferred and used most often. The frequency of pawing increases initially after eating has begun and in some cases becomes quite frantic, often knocking the bucket over. Frequency of pawing declines toward the end of the meal.

It is usually the spilling of feed that concerns the owner who does not want the horse to eat off the ground, worrying that this is unhygienic. Thus owners may attempt to prevent spills by using a high or fixed manger or hanging a feed bin over the door. As the horse then continues its stereotypy, it can knock its knee or fetlock with resulting contusions or other traumatic injuries to the limb. Occasionally, the forelimb may get caught in the bucket handle, causing quite serious injury; the foregoing are the most common instances in which this stereotypy is brought to veterinary attention.

By feeding directly from a cleared area of floor, or on a small piece of rubber matting (for the very hygiene-conscious owner), using a soft bucket, removing bucket handles, or adding the concentrate feed to the forage, many owners avoid further concern from the effects of this stereotypy.

Self-mutilation

It is the physical consequences of this stereotypy that cause the most concern to owners. When aroused or

excited (typically after sniffing at dung, urine, or at other horses, returning to a box or paddock, or mixing with or moving away from other horses), a horse with this stereotypy will sniff, lick, and bite itself to the point of causing injury and granulomatous skin lesions usually on the flank, chest, and forelimb areas. Intensity and frequency varies between individuals, ranging from an occasional lick that may not break the skin to violent head-swinging, snatching and biting, maintaining large open sores. Self-mutilation is most often reported in stallions, although it also occurs in mares and geldings.

Rug-tearing

Stereotypic rug-tearing is probably the same activity as self-mutilation but one in which the rug and not the skin suffers! The damage to rugs may be suspected to be caused by rubbing and scratching indicative of discomfort due to poor rug-fit and cutaneous allergic reactions and infestations without any other associated signs. Alternatively, it may be seen to occur in the situations described above. The pattern and nature of the damage may seem unusual for primary skin irritation, being concentrated along the flank and chest, and with stereotypic rug-tearing, there may also be associated lesions on the forelimbs, especially behind the knees. The activity will also continue, often in a routine fashion, when the rug is removed.

Other Stereotypes

Many other idiopathic behavior patterns can be incorporated into a stereotypy, and the common names for these such as teeth-grinding and tongue-flicking are largely self-explanatory. Intermittent but prolonged tongue protrusion, seen most often in horses in a box but occasionally in some horses while being ridden, in the absence of other pathological signs may also be a stereotypy.

PREVALENCE

Stereotypes have been reported in horses of all ages, including foals, although there is a tendency for prevalence to increase with age.[14] Comparison of the results of a number of surveys shows that stereotypes occur in many different breeds of horses, of all ages and involved in many equestrian disciplines.[12,14–19] Prevalence ranges from 1–26%, with most surveys finding approximately 8% of horses to have some form of stereotypy. For particular stereotypes, prevalence ranges from 0.4–6.8%, with crib-biting plus wind-sucking, weaving and box-walking being the most common. Dietary disorders and learned behavior problems can occur in all types of horses of all ages, with approximately 10% of leisure horses developing behavior problems for which the owner requires professional advice and assistance (in the United Kingdom in the author's experience).

COMMON MISCONCEPTIONS

Observational Learning

Many horse owners believe that horses will copy stereotypes, particularly crib-biting, from each other or that these behavior patterns are learned as a foal from the dam. There is however no scientific evidence for this, and studies investigating such *observational* learning in the horse have failed to show that it occurs.[20] This mistaken belief adds to the common fear of horses with stereotypes and is often responsible for their isolation, particularly being kept out of sight of other horses. This is very distressing for such a highly social animal as the horse[21,22] and is only likely to exacerbate the stereotypy.

Boredom

Boredom is frequently cited as a putative cause of stereotypes. However, this is not consistent with observations on occurrence, as stereotypes are seen in arousing, exciting, and disturbing situations in response to certain stimuli and are not seen in response to a general lack of stimuli. Owners may regard the horse which is suddenly isolated or confined to a box or removed from work as suffering from boredom. However, it is other husbandry changes commonly associated with this situation (such as a change of diet, companions, and exercise routines) that create frustration, along with coincidental factors such as pain or opioid-based analgesic therapy, and affect stereotypy performance here.

Associated clinical problems

Owners are often unaware of the fact that sudden onset or increase in frequency of a stereotypy may

be an indication of pain, stress, or a potentially serious clinical problem requiring veterinary attention. This should be borne in mind when taking a history which primarily presents as a stereotypy (Table 29.2).

As stereotypic behavior is a sign of frustration, arousal, increasing basal β-endorphin and/or cortisol levels, and other physiological changes leading to dopaminergic super-sensitization, particularly in the mesoaccumbal region (see below), the initial therapeutic approach should be to check for, remove, or treat appropriately any physical cause of these. Where self-mutilation is seen in a mare or gelding, hormonal status and HPA-axis function should be checked to eliminate pathological changes as a cause of this stallion-like behavior. However, approximately 30% of geldings and naturally dominant mares show some stallion-like behavioral characteristics and may also develop a self-mutilating stereotypy in the absence of such pathological hormone changes.

ETIOLOGY

The development of stereotypy performance depends on:

- Genetics
- Neurophysiology
- Circulatory β-endorphin levels
- Dopaminergic (DA) super-sensitization
- Critical arousal and current activity

Table 29.2. Clinical Problems That Have Precipitated or Exacerbated Stereotypy Performance in Horses

Pain (via rising β-endorphin levels)
e.g., crib-biting and post-operative pacing
Abscesses (teeth or feet)
e.g., crib-biting and windsucking
HPA (hypothalamic-pituitary-adrenal) axis and granulosa cell tumours
e.g., self-mutilation in mares and geldings
Specific circumstances in foals
Maternal rejection/separation
e.g., for veterinary treatment
Inadequate milk supply
Excessively high-protein creep feed
Acid-indigestion

Genetic Predisposition

The predisposition to develop and perform stereotypes in certain husbandry conditions does appears to be inherited,[15,16,18] and this genetic effect may well have given rise to such suspicions of mare–foal learning. For example, prevalence within affected families rises from 1–26% to 13–67%. This also explains why in the same husbandry conditions only some horses show stereotypes, which may have given rise to the traditional belief that these were *bad* horses.

A number of conclusions have been drawn from examination of family histories from one study of the inheritance of stereotypic behavior patterns in Przewalski's horses (*Equus przewalski*)[23] which is likely to be the same in the domestic horse (*Equus caballus*).[24] The alleles involved were not sex-linked, had recessive characteristics, and appeared to be segregating in a relatively simple pattern, suggesting that very few alleles possibly segregating at a single locus may be involved. The probability of any individual showing a stereotypy under certain environmental conditions rose with the coefficient of inbreeding. Also, where a stereotypy was seen in a grand-dam, grand-sire, or other sibling, the probability that an offspring from a particular sire and dam demonstrated a stereotypy depended on the sire's and dam's behavior. If neither had been seen to perform a stereotypy, this probability was approximately 25%. If either the sire or the dam had been seen to perform a stereotypy, this probability rose to approximately 60%. If both had a stereotypy, then the probability of the offspring developing a stereotypy was approximately 89%.

The stereotypy of the offspring was not the same as that of the sire or dam. Also, many more (73%) affected offsprings came from non-affected mares, and conversely, fewer (27%) of the offsprings from affected mares were themselves affected, supporting the conclusion in other studies[15,16] that maternal effects and mare-foal learning in particular are not involved.

Unless exposed to certain stimuli, a genetically susceptible individual may never develop a stereotypy, and conversely, if sufficiently stimulated any individual could develop a stereotypy. Stereotypes have not to date been reported in feral horses, although there have been many detailed studies of their behavior. In a typical group of horses that have been chronically stressed in certain husbandry

conditions, only those that are genetically more susceptible will develop a stereotypy. These horses can therefore be regarded as useful early warning indicators of such stress. Thus, treatment involving husbandry changes, which can be undertaken to ameliorate the stereotypy, may be beneficial to all of the horses kept in this way.

Neurophysiology

The neurophysiological basis for such genetic variation in susceptibility to stereotypy has been established in some species.[25–29] Such a mechanism is consistent with reported findings to date of stereotypic behavior in the horse and offers considerable scope for treatment. Also, the incidental therapeutic effects of various pharmacological agents on equine stereotypes suggest that genetically predisposed individuals are simply more sensitive to certain forms of dopaminergic and opioid stimulation.[30–32]

In these other species, predisposition to stereotypy development is due to genetically determined variation in activity of dopaminergic neurons. In particular, individuals susceptible to stereotypy development in certain situations have been shown to have greater numbers of, or more active dopaminergic neurons, particularly in the mesoaccumbens and the striatum nigra region of the mid-brain. This results in relatively greater dopamine activity and a lower threshold for opioid-mediated and direct dopaminergic stimulation. Such individuals are also more prone to dopaminergic neuron supersensitization by increasing basal levels of circulatory endogenous opioids, such as β-endorphin, as occurs during chronic stress.[33] As mid-brain dopaminergic activity is responsible for general arousal, alertness, and reactivity, these horses are also likely to be more alert, active, and reactive than others.

Alternatively, an acute rise in β-endorphins as a response to pain or concurrent with acupuncture treatment or considerable physical exertion, or following the administration of exogenous opioid analgesic drugs may precipitate stereotypic performance in any horse. Some horses will only show their stereotypy in such situations as when injured, exhausted, or pleasurably excited for example, and others may show an increase in frequency and intensity of performance at such times.

A diurnal pattern to crib-biting has been reported,[34] which is consistent with diurnal variation in β-endorphin levels[35] and feeding patterns[36] in the horse. Circulating concentrations of β-endorphins rise sharply when eating a palatable feed,[36] explaining the observed incidence of stereotypes such as crib-biting, wind-sucking, and box-walking during feeding. There is however some disparity in reported basal circulatory levels of β-endorphin levels in the horse in association with stereotypy performance. One study reported lower basal levels (approx. 50%) in crib-biting horses.[36] There were also age, gender, and breed differences between this and the control group, however. When controlling for these effects, another study found, as expected, significantly higher (approx. 300%) basal levels of β-endorphin in crib-biting horses (49.5 pmol/L) compared with control horses (16.2 pmol/L).[37] There was a significant effect of age with older horses having higher levels of β-endorphin, which would explain the effects seen in the first study[36] as their crib-biting group had a much higher average age. This is also consistent with the reported general increase in prevalence of stereotypes with age.[14]

Thus the role of endogenous opiates such as β-endorphin would appear to be pre-motivational causing dopaminergic supersensitization via increasing basal levels resulting from chronic stress or by direct stimulation of DA receptors when acutely increased. This should be kept in mind when considering the administration of dopaminergic or opioid agonists and antagonists to horses with stereotypes, as the dose-response pharmacokinetics in these horses may differ from other horses. For example, they are likely to be relatively more sensitive to dopaminergic agonism and relatively less sensitive to opioid antagonism than horses without stereotypes.

Some individuals develop more than one stereotypy.[23] While there are common themes to the etiology of all stereotypes, different behaviors occur in different situations with different precipitating factors,[38] and horses with more than one stereotypy do not do both at once. Thus, it is likely that there are differences in the details of their underlying physiology in the horse as found in other species, for example, where some involve opiates where others do not; some involve D1-type receptors and others predominantly D2 type.[39,40] These differences in underlying neurophysiology are reflected in the efficacy of various pharmacological agents in blocking different stereotypes in the horse and the situations

stimulating their performance. For example, some stereotypes such as crib-biting, wind-sucking, box-walking, and self-mutilation occur when circulatory β-endorphin levels are rising and can be stopped by opioid receptor blockade using diprenorphine[41] and naloxone.[42,43] Others, such as weaving for example that do not occur in these situations, are not affected by opioid antagonists.[43]

Sensitization of mid-brain dopaminergic neurones and consequent lowering of the threshold for stimulation of these will cause affected horses to subsequently show stereotypic behavior in any situation when aroused, excited, or frustrated, whereas before physiological sensitization reached the critical limit, stereotypy was not seen in these situations. This apparent increase in triggering factors or incidence may give owners cause for concern.

While details are complex and much remains to be elucidated, such a neurophysiological mechanism would explain many observations regarding stereotypic behavior in the horse and is consistent with reported findings of the many factors affecting these behavior patterns. Such a mechanism also offers many other options for pharmacological manipulation of stereotypic behavior that have not yet been clinically tested. To date, however stereotypy performance can be considered indicative of relative dopaminergic agonism, particularly of meso-accumbal dopaminergic neurons, directly for some stereotypes (such as weaving) and opioid-mediated for others (such as crib-biting and box-walking). See Table 29.3.

The role of endogenous opiates such as β-endorphin is pre-motivational, causing dopaminergic supersensitization via increasing basal levels e.g., resulting from chronic stress or by direct stimulation of DA receptors when acutely increased, e.g., resulting from pain or the ingestion of highly palatable feedstuffs. Therefore pharmacological *blocking* does not raise the same welfare issues as physical prevention which is post-motivational and therefore frustrating, and it is reasonable to use pharmacological support in some cases where the stereotypy causes harm or poses particular safety risks. This explains the pharmacokinetics of opioid antagonist blockade of stereotypic behavior and contrast with the learning curve seen when hay-dipping is resolved by providing soaked hay.

Physiology

Horses susceptible to stereotypes have different physiological backgrounds to others. This would explain the common observation that horses with stereotypes are more alert and reactive and can be more difficult to sedate than others.

Horses prone to stereotypy show a marked startle reaction (dopaminergic response) after only 10 minutes or so of being twitched, in contrast to others which do not react to the rising β-endorphins from the twitch until about 25 or 30 minutes have elapsed. As the benefits of peripheral pain relief due to the rising β-endorphin from the twitch are not maximized until 7 or 8 min, the window of opportunity for procedures in stereotypy prone horses is very slight. This is why horses prone to stereotypy will usually be much more difficult when restrained by twitch, and this mode of restraint is therefore not recommended for these horses. Heart rate also shows a transient but marked increase at the critical point of dopaminergic agonism here after circulatory β-endorphins peak (up to 200 bpm). The use of a heart rate monitor gives the handler the chance to get out of the way just before the reaction occurs.

Table 29.3. Key Points Regarding the Neurophysiology of Various Equine Stereotypical Behaviors

- Chronic stress increases basal circulatory β-endorphin levels
- Rising basal β-endorphin results in dopaminergic super-sensitization, particularly in mesoaccumbens
- Some horses are more susceptible to this than others due to genetically determined greater numbers of DA neurons with a lower threshold for stimulation.
- Acute stress can directly involve DA neur ons in mesoaccumbens
- Some stereotypes involve D-type receptors and others predominantly D2-type
- Increased β-endorphins are a cause not an effect of stereotypy performance

This offers a simple method of testing horses—those prone to stereotypy in common husbandry systems will show the sudden startle response (e.g., head up, muzzle out, ears pricked, wide-eyed) and leap forward after the twitch has been on for about 10 min. Those which are not will last for around 25–30 min before showing this reaction.

Traditionally, stereotypes were classified according to the nature of the activity involved. For example, box-walking and weaving were classified together as *locomotory* stereotypes and crib-biting and self-mutilation as *oral* stereotypes.

Recent research however has shown that those stereotypes which occur during eating, such as crib-biting and box-walking, are opioid-mediated and can be blocked by opioid antagonists. These compounds are ineffective in the treatment of other stereotypes such as weaving for example, which are directly dopaminergic, being blocked only by direct dopamine antagonists. This therapeutic classification (i.e., opioid-mediated or directly dopaminergic) is more useful, offering a predictive treatment option for any new stereotypy. Stereotypic behavior, such as crib-biting and box-walking for example, precipitated by offer of a treat, seen when eating and increasing immediately after eating are opioid-mediated and are likely to be blocked by opioid antagonists. By contrast, stereotypic behavior, such as weaving, precipitated by acute frustration from social restriction or in anticipation of feed is directly dopaminergic and not affected by opioid antagonists, requiring direct dopaminergic antagonism or serotonergic agonism.

Husbandry

Many husbandry factors have been suggested as putative causes of the chronic frustration leading to stereotypic behavior. These include low fiber, high-protein diets, physical and social restriction, and lack of exercise.[2,44,45] These factors are often confounded, many varying together making underlying evaluation of the contribution of each difficult. However, from a series of studies feeding the same group of horses many different diets which were carefully compiled to vary in only one factor at a time, it has been shown that time spent feeding is one of the most important key factors in determining the amount of time spent performing stereotypes in the horse.[46] For example, in this study, horses fed a highly fibrous diet, which was mechanically processed in order to substantially decrease consumption time, showed considerable abnormal behavior.[46] The percentage of any 24-hour period spent in stereotypic behavior (AB) has been predicted from the percentage of the same period which horses spent eating (F) with a high degree of accuracy ($R = 0.98$), according to the exponential equation $AB = 123.3\ e^{0.07F}$. This relationship explains the well-known beneficial effect of feeding more fiber,[2] as high forage-based diets usually require much greater consumption time than diets containing a high proportion of concentrates. The effect of time spent eating explains many of the findings of a survey of management factors associated with an increased amount of abnormal behavior in thoroughbred racehorses, where this risk increased when the amount of forage fed was less than 6.8 kg/day when bedding other than straw was used and when hay rather than other forages was used.[19] Straw bedding may be eaten when dietary fiber is otherwise restricted. The most commonly used alternatives to hay such as haylage, silage, horsehage, alfalfa, and various chopped mixtures of the above with straw have a much lower dry matter content and/or much shorter fiber length than hay, which will considerably increase the time required to consume daily-nutrient requirements. The chops used as alternatives to hay are also commonly fed in small-holed haynets (for practical reasons), which will also increase consumption time. Once feeding time falls below 12 h/day, there is a considerable increase in the amount of time spent in abnormal behavior.

The second most important dietary factor is the relative balance of serotonergic and dopaminergic neurotransmitter precursors, as this directly affects the relative activity of these catecholamines and subsequent activity.[47] As already discussed, relatively more dopaminergic activity, particularly in the mesoaccumbal region of the mid-brain, will facilitate stereotypy performance.[29] Thus, a greater relative amount of tyrosine and phenylalanine (dopamine precursors) to tryptophan (serotonin precursor) in the diet will produce more stereotypic activity. Furthermore, transport across the blood–brain barrier for such large neutral amino-acids is competitive, and tryptophan tends to be relatively rare in most dietary proteins. A high-protein meal will therefore effectively reduce the plasma tryptophan:tyrosine ratio. Feedstuffs commonly

used to increase the protein content of equine diets, such as oats, maize, and peas or beans generally tend to have relatively lower tryptophan content than other lower protein feedstuffs. For example, it can be calculated that maize, pea meal, bean meal, soya meal, and oats have typically 6.0, 8.0, 10.0, 12.0, and 13.0 ma of tryptophan per kg crude protein respectively. Thus, feeding protein in excess of requirements (656–1427 gCP/day for a 500 kg horse[48]) and using feedstuffs such as maize, peas, and beans may exacerbate stereotypy in a genetically predisposed horse. As dopaminergic activity is also responsible for general alertness and reactivity, this mechanism also offers an explanation for the commonly perceived effect of these feedstuffs in contributing to excitability and general handling difficulties in the horse.

Sweet or highly palatable feedstuffs will enhance stereotypy by the resultant increase in plasma levels of β-endorphin, stimulating dopaminergic activity and the performance of opioid-mediated stereotypes such as crib-biting and box-walking, for example, are commonly observed during and immediately after feeding.

As horses are strongly social animals, showing considerable distress when isolated,[21,22] the social restriction imposed by keeping horses individually in loose boxes has often been suggested as another key husbandry factor in stereotypy development,[2] and indeed, box design minimizing contact between neighboring horses was found to be a significant factor increasing the risk of abnormal behavior in a survey of thoroughbred racehorses.[19] This survey found there to be no reduction in this risk when sniffing or touch was possible in addition to visual contact, concluding that visual contact alone may be adequate. However, the survey did not include horses that had full physical contact with an element of free association or social choice (e.g., as when loose-housed together) and so the potential extra benefits of such further contact could not be fully evaluated. Another study found that physical confinement was relatively unimportant in determining the time spent in abnormal behavior in comparison with dietary changes and social restriction.[46] Horses in typical tie-stalls have much greater social contact than those in typical loose boxes, which might explain why some horses will weave in a loose box but not in the more physically restrictive tie-stall, all other conditions being similar. Similarly, social isolation may play a major role in the weaving seen by some horses only when traveling. Horses that tend to form strong relationships with very few other individuals, or one other horse in particular, appear to be particularly susceptible to social isolation stress and may be more likely to develop a stereotypy such as weaving when removed from such preferred companions.

Thus, less time spent feeding (<12 h/day) a high protein, relatively low-tryptophan diet, and social restriction appear to be the key husbandry factors in the development of stereotypes in the horse.

A number of other husbandry-related factors also contribute. When horses become less fit, for example due to a sudden decrease in work and exercise, basal β-endorphin levels rise, facilitating stereotypy performance and offering another mechanism for the common casual observation and concern expressed by owners that horses confined to their box may increase stereotypic activity. However, there are many other factors in such a situation, such as increased frustration, social restriction, dietary change, pain, and use of opioid-based analgesics that might all contribute to this observation. Less time spent feeding and social restriction represent chronic frustration for the horse. Other forms of chronic stress or acute frustration from husbandry practices, such as weaning, when routine is disturbed, when moving home, breaking or starting schooling, re-schooling and so on are also likely to precipitate stereotypy performance in the genetically susceptible horse (mediated by increasing cortisol levels, Pro-opiomelanocortin (POMC), basal β-endorphin levels, and dopaminergic supersensitization).[49] Similarly, acute stress such as sudden and prolonged isolation, extreme fear, excitement or a combination of these factors may precipitate stereotypy in any individual, and any factor increasing frustration, arousal, β-endorphin levels, and dopaminergic stimulation may contribute to stereotypy development. These factors are most likely to occur around weaning, when sold, or when training and work is began and typically stereotypy may initially be seen.

Effect of Current Activity

Early work on amphetamine-induced stereotypy in a variety of species found that the activity of the animal and the shape of its enclosure at the point of critical dopaminergic stimulation resulting in

stereotypy determined the nature of the stereotypy.[50] The particular action that was repeated and became the stereotypy was most likely to be specific elements of whatever the animal was doing at the moment when this stimulation and arousal reached the critical limit. Should such a mechanism occur in the horse, this would explain many common observations on the nature of equine stereotypic behavior patterns. For example, self-mutilation is most often seen in stallions, and it is stallions in particular which are most likely to become highly aroused when sniffing and licking dung, urine, and certain areas of the body such as the flank and forearms, as part of their normal social behavior. A mare or gelding with other behavioral characteristics of social dominance or hormonal disorders would also be particularly aroused by this kind of activity. Such influence of the current activity on stereotypy development would also explain the casually reported increased incidence of box-walking in endurance horses on the evening after an event. Endogenous β-endorphin levels rise on exertion, and it is likely that these horses will have been walking or jogging when these reached a critically high point during the race. This would also explain the finding in one study that box-walking was more prevalent in Arabians (7.3%) compared with 1.6%, 0.6%, and 3.5% for pleasure horses, standard-bred, and thoroughbred stables respectively.[14] Similarly the rein-snatching often seen in race horses as they are being led back to the collecting ring after a race is a stereotypy comprised of elements of attempted bit evasions and threats to neighbouring horses. These are most likely to occur when being held straight or when they are jostling for position during the race, when β-endorphin levels are rising and may reach the critical levels required. A highly palatable concentrated feed, with ensuing increase in β-endorphin levels, may in the same way precipitate a stereotypy such as crib-biting, consisting of isolated elements of normal feeding behavior. Should a horse become frustrated when left alone in a box, anxiously looking out for companions or excitedly awaiting a palatable feed, a stereotypy incorporating elements of this such as weaving may develop, and this would be consistent with the incidence of these particular stereotypes.

Such a mechanism is also consistent with the general finding that in other species the stereotypic behavior is usually structurally or morphologically similar to the activity the frustration of which is considered to be a causal factor,[3] without requiring the problematical extrapolation that the stereotypic activity is an attempt to make up for that frustration (e.g., provide the sensation of movement or eating when movement or feeding is restricted in some way), as this is not borne out by experimental findings. In one survey, for example, horses with bedding other than straw were found to be more likely to weave, but not to be more likely to perform other abnormal behavior such as crib-biting, box-walking, or wood-chewing.[19] Straw was considered to provide extra fiber and oral satisfaction and the lack of it thought to be more likely to induce an oral-based stereotypy. However, straw encourages a horse pottering around the stable, to pause and investigate as he turns up interesting smells and pieces of grain etc. Horses without straw are more likely to be found standing at the door of the stable, looking out, and so may be more likely to be doing this when dopaminergic sensitization and arousal reach the critical point for stereotypy development, and so their stereotypy will be composed of these elements of this activity, i.e., weaving. This might also explain the remedial value of companions and greater social choice which appears to be particularly effective for horses which weave and why some horses will weave in a loose-box but not in a tie-stall. Should the weaving not be an attempt to increase the sensation of movement when physically restricted, but rather simply be what that horse was most likely to be doing (i.e., peering out of the box, watching, trying to maintain contact with others) when critically aroused?

Some horses when pacing will follow a particular pattern (e.g., two steps to the left, six to the right) even to the extent of initially crashing into the wall if placed in a new box where it is physically impossible to carry out the original routine (e.g., there is not enough room for six steps to the right). Where box designs, such as size or the position of the door for example, are sufficiently different this can often be used to determine whether or not stereotypic pacing could have developed in the new box after a horse was sold or was more likely to have developed in the old box, prior to sale.

Likewise, pacing or box-walking horses may appear to step or trip over, move around or sniff at non-existent objects or stop and turn as if to look out where there is no window, lending a bizarre element

to the stereotypy, causing concern perhaps for sensory perception, motor activities, or coordination. In the absence of other morbid pathology or other clinical signs, this unusual aspect of some stereotypes may be explained by the influence of current activity on stereotypy development, should appropriate objects and stimuli have been there in the box when the horse was pacing around at the point when he became sufficiently aroused to precipitate stereotypy. Such a mechanism also offers an explanation for the predominance of elements of the most common behavior patterns, such as feeding and locomotion for example, in stereotypic activities.

Once one stereotypy has developed, a horse will tend to perform this particular activity when stressed or aroused as previously described. There are also a number of horses which perform more than one stereotypy, key triggering factors being different for each and they do not do both at once. Generally one activity is the most common, with the other appearing when even more severely stressed or aroused. It is possible that if further aroused whilst carrying out another activity, when conditions do not allow performance of the first stereotypy (further adding to frustration and arousal) that this second activity is repeated and becomes another stereotypy. This idea is consistent with the casual observation that when physically prevented from carrying out a particular stereotypy, such as weaving by use of an anti-weaving grille, the horse may develop another, such as head-twisting or box-walking instead. This would also explain the finding of a significantly greater proportion of horses with more than one stereotypy in Przewalski's horses (*Equus przewalski*)[18,21] with a history of considerable confinement, relocation, and frustration, compared with other similar studies of related individuals,[15,16] although this could also represent species differences between equids in susceptibility to stereotypy development.

Thus, the nature of the stereotypy gives a clue as to the particular activity of the horse at the time when dopaminergic stimulation reached the critical point for stereotypy development, with increasing arousal, and/or β-endorphin levels. This might be of use in a dispute involving the sale of a horse which is claimed not to have shown this behavior in the old environment but does show it in the new. The nature of the stereotypy cannot, however, be used to infer what aspect of his environment is lacking or responsible for the frustration, stress, or excitement leading to arousal, sensitization, and stereotypy development.

STEREOTYPIC BEHAVIOR IN THE FOAL

Although there is an increasing prevalence with increasing age, stereotypes are seen in foals and have been reported in a foal as young as 8-weeks-old which used his dam's hocks for crib-biting.[44] Maternal rejection, lack of adequate milk supply, reduced suckling time, lack of access to creep-feed, bullying by others, inadvertent separation from the mare or separation for veterinary attention, pain, opioid-based therapy and possibly a very high protein creep-feed (e.g., >18% CP) containing a relatively high proportion of low tryptophan feed-stuffs (such as maize, peas, beans, soya, or oats) are all potential causes. When seen in foal at foot with the mare at pasture, where the foal shows no other morbid pathological signs and is growing as expected, particular care should be taken to check for injury or other sources of pain. It is also important to observe maternal and other social interactions including access to any creep-feed to ensure that as many sources of frustration and arousal are eliminated as causal factors. It is then possible to conclude that the stereotypy seen may be the result of extreme pleasurable arousal, a response to increasing endogenous opiates after suckling, or other excitement in a foal with a genetically high predisposition to stereotypic behavior. In this case, it would be expected that at least either the dam or sire, and usually both, also show stereotypy although it may not necessarily be the same as that of the foal.

PRECIPITATING FACTORS

Horses genetically susceptible to stereotypy do not perform their stereotypy constantly. Particular events in the daily routine and certain events which occur in most horse's lives trigger stereotypy performance. Some horses have more than one stereotypy. Each occurs at different times, is triggered by different external factors and they do not do both at once. Key factors precipitating stereotypy performance are arousal and increasing β-endorphins. These commonly result from:

- Frustration (increasing arousal)
- Excitement (increasing arousal)
- Chronic stress (rising basal circulatory β-endorphin)

- Acute stress (directly dopaminergic arousal)
- Pain (rising β-endorphin levels)

See Table 29.4.

Routine husbandry practices such as weaning, starting schooling, training, and changing routine can all precipitate stereotypy performance. When a horse is sold, many of these events occur together and it is possible for a horse that showed no signs of stereotypy in the previous environment to show this immediately upon arrival in the new environment. The manner in which the stereotypy is carried out is instantly typical and can appear spuriously *well-practiced* the first time it is seen, and you should look for the physical signs described above to form an opinion regarding when and where the stereotypy developed.

FUNCTION OF STEREOTYPIC BEHAVIOR

Stereotypic behavior was at one time defined as *having no obvious goal or function*.[3] However, further study of causation and underlying physiological mechanisms has given rise to various hypotheses on function, and in the horse there is an increasing amount of experimental evidence supporting the theory of de-arousal as a positive function for this behavior.[51,52] Such a function would also explain the most outstanding definitive characteristic of stereotypic behavior patterns—their repetitive nature—as repetitive activities produce predictable feedback that is well known to have a calming or de-arousing effect.

This raises serious ethical difficulties regarding traditional attempts to treat stereotypic behavior, based on simple prevention via physical or surgical means, which are now regarded as extremely detrimental to welfare. Horses so treated are only likely to be further frustrated, further increasing arousal, basal cortisol, and β-endorphin levels with consequent immunosuppression.[37,53] Horses may also show increasing aggressiveness and handling difficulties and are more likely to develop a different stereotypy to that which is being physically prevented.

Table 29.4. Management and Husbandry Conditions Which Precipitate Stereotypical Behaviors in Horses

- Anticipating feed
- Eating
- Horses in yard leaving or arriving
- Leaving familiar horses or handlers
- Meeting new horses or handlers
- Turn-out into a paddock or new box
- When isolated including for traveling
- Weaning
- Sale
- Any change of routine
- Increasing palatable feed
- Increasing protein content of feed (relatively less tryptophan)
- Lowering relative tryptophan content of feed
- Acupuncture (rising β-endorphins)
- Surgery (pain and postoperative opiate-based analgesia)
- Increasing work (rising β-endorphins)
- Reduction in fitness (rising basal β-endorphins)

TREATMENT

As stereotypic behavior can be considered to be a sign of frustration, arousal, pain, increasing basal β-endorphin and/or cortisol levels, and other physiological changes leading to dopaminergic supersensitization, the initial therapeutic approach should be to check for, remove, or treat appropriately any physical causes of these factors. Where self-mutilation is seen in a mare or gelding, their hormonal status and HPA-axis function should be checked to eliminate pathological changes as a cause of this stallion-like behavior. However, approximately 30% of geldings and naturally dominant mares show some stallion-like behavioral characteristics and may also develop a self-mutilating stereotypy in the absence of such pathological hormone changes.

In the absence of any such obvious direct physical causes, there are a number of treatment options to be considered, that of choice being specific and permanent husbandry change. The overall aim of any treatment program is to reduce relative mesoaccumbal/striatal dopaminergic output. As there are many common aspects in etiology of various stereotypes, a similar approach is likely to be beneficial to all, although there are of course some underlying physiological differences between individual stereotypes requiring individual therapeutic approach (Table 29.5).

Selective Breeding

This is likely to be an unpopular solution as it can be calculated that a high proportion (approximately 40%) of the non-affected population will be carriers, and many horses with stereotypes also have other highly desirable qualities, contributing to considerable competitive success and financial value. Owners wishing to breed from a horse with a stereotypy should, however, be aware of the increased likelihood of producing offspring with a stereotypy.

Furthermore, horses which have a genetically determined lower threshold for dopaminergic sensitization and show stereotypic behavior when relatively less stressed, frustrated, or aroused than others can also be regarded as extremely useful early-warning indication of inappropriate husbandry and, as such, removing these from the general population could be regarded as detrimental to equine welfare in general.

Husbandry and Management

In the absence of any direct physical causes, there are a number of treatment options to be considered, that of choice being specific and permanent husbandry change. The overall aim of any treatment program is to reduce relative mesoaccumbal/striatal dopaminergic output. As there are many common aspects in etiology of various stereotypes, a similar approach is likely to be beneficial to all, although there are of course some underlying physiological differences between individual stereotypes requiring individual therapeutic approach.

Table 29.5. Summary of Treatment Recommendations For Horses with a Variety of Stereotypical Behaviors

- Increased time spent feeding
- Avoid bucket feeds
- Feed more fat, less starch
- Reduce pH of digesta—acid suppressants
- Feed high-tryptophan proteins
- Do not feed protein in excess of requirements
- Improve social contact
- Avoid routines
- Increase fitness
- Use harem-based breeding
- Use cribbing comforter and protect teeth from hard surfaces
- Use diary to quantify progress
- Use Y-type cribbing strap only as a last resort before euthanasia

In a typical group of horses that have been chronically stressed in common husbandry conditions, only those that are genetically more susceptible will develop a stereotypy. These horses can therefore be regarded as useful early warning indicators of such stress. Thus, treatment involving husbandry changes that can be undertaken to ameliorate the stereotypy will be beneficial to all of the horses kept in this way.

The aim of therapeutic husbandry change should be to provide a calm, frustration-free environment for the horse where he can fully express all of his natural behavior patterns.[2] Turn-out in a large group (>25) of horses (of mixed age and gender) onto extensive rough pasture (>1 acre/horse) fed with forage *ad libitum* when required, with supplements only if necessary to achieve nutrient requirements, would eventually (e.g., in >6 months) eliminate stereotypic performance. With careful design, loose yarding in well-chosen groups of around 6 horses with stocking density 30 m^2/head can be an adequate substitute. However, this sort of change is impracticable for most horse owners.

The most effective method is to increase time spent feeding to more than 12 h and up to 18 h/day (24-hour period). When a high proportion of the day is spent performing stereotypes, even a very small increase in time spent feeding will have a considerable effect in reducing stereotypic performance. Obviously, feeding a high forage-based diet will maximize time required for consumption. Many owners underestimate the feed value of forages and greatly underutilize this very cost-effective feedstuff. For example, most horses will consume 2–2.5% of their body weight (in DM/day), and the average 500 kg Thoroughbred in light work will receive all of his nutrient requirements from good hay (e.g., 9–10% crude protein) fed *ad libitum*. For growing horses or those in harder work, where such a highly fibrous diet will not meet all of the nutrient requirements, or where the increased hind-gut mass associated with such feeding is considered to hinder athletic performance, time spent feeding can be increased by physical manipulation of the ration.[54] Chopping or reducing fiber length (e.g., to ~10 mm)

and soaking (e.g., by complete immersion for at least 30 min), and where pellets are fed, using the softest, longest pellets available (e.g., up to ~10 mm) will all increase consumption time.[55, 56] Horse type also affects consumption time; larger horses, such as Thoroughbreds, with their greater breadth of incisor arcade were found to take less time to consume a given amount of trial feedstuffs than smaller ponies, such as the Shetlands.[54] Some indication of probable consumption times can be offered from the results of a study where a group of 5 Thoroughbred horses took an average of 53, 91, and 67 min to consume either 1kg DM of long dry hay (mean fiber length 33 cm), 1 kg DM of the same hay chopped (mean fiber length 4 cm), and kg DM of the same hay soaked for 30 min, respectively.[54] Thus, in this study chopping was more effective than soaking in increasing ingestion time.

Considerable individual differences, however, were seen in ingestion rates, ranging from 20–96 min/kg hay in another study,[56] and where an accurate prediction of the likely improvement is required, the horse concerned should be observed and ingestion rates recorded directly over a few days.

Time spent feeding can also be considerably increased by decreasing the accessibility of the feedstuff, for example, using small-holed haynets or even a sac made by placing four of these inside each other, so that the horse has to spend much more time extracting the hay or forage from the net. By using a number of such sacs placed in different corners of the box or enclosure and dividing the daily ration between each, the horse may be encouraged to choose and move between nets, further increasing consumption time. These methods of increasing time spent feeding will also encourage oral and locomotor activities with elements of ingestion and selection similar to grazing, which may further help to reduce frustration in the stabled horse. An operant device, which the horses have to work for food by pressing a plate, thus increasing time spent feeding and so likely to reduce stereotypy performance, has also been described.[57] Care should be taken however not to increase the time required to consume particularly palatable food too much as this can lead to frustration and exacerbate stereotypy performance.

Care should be taken not to feed protein in excess of requirements and whenever possible, to choose a protein source relatively high in tryptophan and lower in tyrosine and phenylalanine. Dried grass, in the form of grass nuts (available with CP up to 18%) would be preferable in this respect to concentrates using maize, pea and bean meal, soya, or oats as the protein source. Rice bran, rice bran oil and, pumpkin seeds are all excellent sources of L-tryptophan.

By sprinkling the concentrate ration throughout the forage, a large high-protein and highly palatable meal can be avoided, thus improving the relative rate of tryptophan uptake and avoiding bursts of increasing β-endorphin levels. Such practices also remove the very exciting, arousing, and frustrating period of feeding-time, a common trigger for stereotypy performance. Devices offering the concentrate feed to be extracted in very small amounts may, however, only serve to increase frustration and are likely to increase stereotypy performance in some horses, as was found in one study of a foodball for horses.[58]

Increasing social contact, particularly allowing the horses to choose their neighbors and giving opportunities to express social behavior such as mutual grooming (which has a calming effect, slowing heart-rate),[59] is also likely to considerably reduce stereotypy performance. Loose yarding, choosing individuals that mix well together without bullying, can be very effective for some animals. Stalls may help where space is restricted, and in any case owners should experiment with neighbors and companions to find which individuals will settle best with each other. Increasing social contact appears to be particularly beneficial for horses that weave. For singly kept horses where this is not possible, a small pony, sheep, goat, calf, or any other species is often accepted as a companion, and it has been suggested that safety glassmirrors may also be a promising alternative. Horses that have to be isolated for clinical reasons may respond even to such items as a rug or tail bandage from a stablemate or other familiar horse if this can be left with him in lieu of company. Of course, increasing familiar human interaction can also be invaluable.

Increasing exercise is often suggested as beneficial in reducing stereotypy performance. It has been shown that as fitness levels increase, basal β-endorphin levels fall in the horse after a slight initial rise when stressed by the increasing work to improve fitness.[60] Thus, increasing exercise might initially increase stereotypy performance but will reduce this as fitness improves. Loose-schooling horses together or riding out in company might also

help by increasing (if only a little) social contact. It is emphasized that there may be considerable individual differences in effective social contact, as companions that excite, bully, harass, or ignore the affected horse may exacerbate rather than ameliorate stereotypy, and owners should be encouraged to experiment with a variety of companions.

For the self-mutilating stallion, a harem-based breeding system, allowing him to run at pasture with the mares he is to serve, may involve less frustration than typical in-hand breeding systems, and there may be individual variation as to which method of breeding best suits each horse.

Maternal pheromones are supposed to have a calming effect and have been used successfully by the author in local sprays to reduce crib-biting frequency during and immediately after feeding.

Owners should be encouraged to evaluate very carefully their reasons for stabling and separating horses in the first instance. Modern rugs and adequate feeding (particularly if this is mainly forage-based) offer excellent protection from adverse climatic conditions,[61] and in extreme conditions, extra feed, open-fronted windbreak shelters, or shades within the paddock may suffice. Most horses, if offered the choice, will leave their stable, and owners should be encouraged to take a less anthropocentric and more horse-centered approach to husbandry systems.

Owners should be reminded that all of these husbandry changes require time to become effective. Change and novelty is itself exciting and arousing, particularly for animals that are being turned out at pasture with company after being stabled alone. Thus, initially for a week or two immediately after husbandry change, stereotypy performance is likely to increase. It should, however, begin to decline thereafter, requiring up to several months before being eliminated altogether. Encouraging owners to quantify and record the frequency of occurrence and intensity of the stereotypy before treatment begins and at intervals (such as fortnightly, for example) thereafter will facilitate compliance and perseverance with the program of husbandry change.

For crib-biting horses, where the owner is concerned about tooth-wear or stable damage, the use of a *comforter* is recommended. This is a device specially made to be safe and convenient for crib-biting—key design features being solidity and a flat gripping or pressing surface at approximately sternum height that will not damage teeth or be excessively worn by use. Wood covered with rubber (from old conveyor belts, flooring, or tires) is ideal. The comforter can be permanently attached to the stable walls, manger, or door where these are solid. Owners may prefer to site this in a less-obvious corner of the box. A short piece of material, (1 ft. long by 4 sq.in.) is usually adequate to provide a cribbing ledge. An old fence post attached to a heavy base covered on top with rubber makes an ideal free-standing and therefore mobile comforter, which can also be used outside. The horse will most likely use the comforter if it is placed beside his feeding place, and particularly if he is first presented to it in a new box (e.g., swap boxes with a neighboring horse, if possible). This is most effective where the part of the box that was previously used for crib-biting (such as the door for example) is sited in a different location relative to the manger or haynet in the new box (Figure 29.2).

The horse should be immediately led across to feed or given treats while being held loosely beside the comforter and not allowed to reach any other part of the stable to crib, except upon the comforter. Smearing this with a sweet, highly palatable substance such as treacle, molasses, or syrup initially for the first week or so will also encourage use. Instead of being concerned about the horse still cribbing, owners are often pleased that he is using the comforter, reducing environmental damage, and are more likely to continue with the therapeutic program.

A similar *damage limitation* approach such as the wearing of specially reinforced rugs (incorporating light metal mesh) might also be beneficial for self-mutilation.

Pharmacologic Treatment

Owners often, however, wish to see an immediate cessation of stereotypy, and in some cases it is also desirable to prevent continuing injury in self-mutilating horses or the danger from a horse that weaves violently when in a trailer making riding hazardous.

Research is only beginning to fully investigate a pharmacological approach to the treatment of stereotypic behavior, particularly making use of serenics such as Buspar and Prozac (which may decrease relative dopaminergic output by increasing serotonergic activity). There is a limited amount of information



Figure 29.2. A horse cribbing on a surface which has been covered with thick rubber to protect both the horse and the surface from excessive wear.

available on the behavioral effects of various drugs in the horse. Hence, the pharmacological approach to stereotypy treatment of horses is largely based on the coincidental effects of various opioid and dopaminergic antagonists on stereotypic behavior discovered whilst carrying out other studies, and by extrapolation from studies in small animal work.[62]

For example, it has been found that 1 ml of 1.5–3 mg/ml IM diprenorphine (hydrochloride) reduced box-walking for up to 3–5 h after injection (with the greatest reduction seen 2–3 h after injection) in two horses.[41] Tricyclic anti-depressants such as imipramine and clomipramine at levels of 500–1000 mg bid orally in grain have been reported to reduce self-mutilation in stallions, with maximal effects after 8 days of treatment.[63] This may work by a mechanism similar to that thought to be involved in the efficacy of such drugs in the treatment of depression—by initiating membrane transport changes preventing the re-uptake of 5 hydroxy-tryptophan that requires several days before becoming effective in increasing relative serotonergic activity.[64] Acepromazine (maleate) at 0.4–0.1 mg/kg IV or IM (K. Houpt, pers comm, 1995) has reduced a number of stereotypes and acepromazine (maleate) at 33–50 µg/kg IV eliminated suspected opioid-induced post-operative pacing (E. Clutton, pers comm, 1994). Naloxone IV eliminated crib-biting with a dose-related effect on latency of onset and duration of effect. At 0.02 mg/kg, 0.03 mg/kg, and 0.04 mg/kg, with a latency of onset of 19, 23, and 12 min crib-biting was blocked for 21, 19, and 11 minutes.[43] It should be noted, however, that naloxone at 0.75 mg/kg IV produced an acute abdominal distress syndrome similar to spasmodic colic in the horse.[65]

Naltrexone at 0.04 mg/kg IV blocked crib-biting between 1.5–5 h with a latent period of 5–35 min and this cessation was maintained for up to 48 h after a 45 min latent period by subsequent subcutaneous (SC) implantation of 0.6 g naltrexone.[43] With a dose of 0.4 mg/kg IV, crib-biting was blocked immediately for 7 h.[43] Nalmefene given IM, IV, or SC at various dosages from 0.08–4.0 mg/kg further extended the effect for a couple of days and for up to 7.5 days when given IV at 10 mg/h.[43]

The effects of opioid antagonism support a pre-motivational role for endogenous opiates such as β-endorphin in some stereotypes, particularly as no frustration-related activities were recorded after administration and when resumed, stereotypic behavior was performed at a similar rate to that prior to administration.

In one study, weaving was not affected at all by opioid antagonists.[43] While dopaminergic antagonism is likely to affect all forms of stereotypic behavior, opioid antagonism appears to be effective only for some. This is consistent with the pre-motivational role of opioid involvement in those stereotypes such as crib-biting and box-walking that are seen during eating or stimulated by a palatable treat, when opioid levels are rising. It also confirms the lack of opioid involvement in other stereotypes such as weaving, which are not seen in these situations.

It has been noted that repeated naloxone treatment in some species has little or no effect on some stereotypes that have been going on for an extended time.[66] This may reflect the development of tolerance or be exacerbated by the increase in basal levels of β-endorphin with age. It has also been suggested that opioid antagonists may only be effective during the period of stereotypy development, perhaps when dopaminergic neurones are undergoing super-sensitization by rising β-endorphin levels. Once sensitized, direct dopaminergic stimulation might then be enough to induce stereotypy performance. No such effects or tolerance have however been reported during naloxone therapy in the horse for periods up to 6 months.[43] With diprenorphine, a significant increase in feeding behavior was seen

immediately in the treated horse,[41] and appetite changes may be an important long-term consideration. One study[43] noted that horses treated with opioid antagonists were capable of being ridden without any adverse effects. As opioid antagonists have many other effects, including sedation, albeit at relatively higher doses, extreme caution is advised when handling or riding any horse so treated.

Tryptophan in a purified powder form given in grain at a dose of 1–3 gms bid–tid was found to eliminate some stereotypic behavior patterns[67] and when given at a dose of 0.1 mg/kg in a concentrated liquid fed on a sugar lump, the head-twisting stereotypy ceased for approximately two hours, with the onset of this effect occurring approximately two hours after administration.[22] There is considerable disparity in effective dose between these two reports. This may be due to a great many differences between the horses and stereotypes involved, but the difference in method of administration is of particular interest. There may have been some direct absorption of the concentrated liquid tryptophan via mucosal membranes, thus avoiding hepatic conversion and consequent decrease in relative tryptophan ratio. Alternatively, the absence of other protein-based feedstuffs when given on a sugar lump instead of with the regular feed would have increased the relative ratio of circulatory tryptophan to the other non-albumin bound amino acids, giving a preferential rate of transport for tryptophan across the blood–brain barrier, enhancing the serotonergic effect and allowing a much smaller dose to be effective. Any dietary factor enhancing insulin release will also result in a much greater uptake of albumin-bound tryptophan. As tryptophan is simply an amino acid and a normal constituent of equine diets, there may be no special consideration for the competing horse.

Nonetheless, the agents used have many different physiological effects. The complex pharmacokinetic effects and wide individual variation in dose-response coupled with very little published information on the therapeutic effects of these agents in the horse present considerable complexities in a pharmacological approach to elimination of stereotypic behavior. As with all such therapies, there are contraindications, potential side effects, and particular considerations for the competing horse. As intervention here is likely to be pre-motivational, treated horses showing no signs of frustration or distress in association with pharmacological blockade does not raise the same ethical difficulties as the traditional approach of physical prevention. However, with careful consideration of the risks involved and close monitoring of individual dose-response, pharmacological support in the short term may be a useful adjunct to husbandry change, dealing with crisis by quickly eliminating the stereotypy and encouraging owners to persevere with the treatment. For some stereotypes, notably that of self-mutilation, although husbandry change has been shown to be effective,[68] the use of orally administered clomipramine may be particularly useful for the breeding stallion, where arousal and frustration are to be expected and arousal desirable.[67]

Ineffective Treatments

Traditional attempts to treat stereotypic behavior based on physical prevention (e.g., weaving grilles, cribbing straps, surgery) or aversive conditioning (eg creosote on surfaces, electric shocks) are now regarded as detrimental to horse welfare. Horses so treated are only likely to be further frustrated, increasing arousal and β-endorphin levels with consequent immunosuppression. They may also show increasing aggressiveness and handling difficulties and are more likely to develop a different stereotypy to that which is being physically prevented.

A variety of devices (stable toys and food balls) are often marketed with the claim that they may help reduce stable-vices. These do not; they are a hazard in the stable and only serve to further increase frustration and β-endorphin levels due to the highly palatable nature of the feedstuffs commonly used.

Aversive conditioning based on punishing the horse, for example, by electrical shock when trying to grasp a surface for crib-biting, is ineffective[44] and completely inappropriate. Stereotypes are not learned behavior and so the horse cannot be conditioned not to perform these by being punished for doing so. The horse may however learn where he may carry out this behavior and although electrified wiring of all available surfaces in a box may initially prove a deterrent, the horse will continue to crib-bite elsewhere or develop another stereotypy. Such attempts at deterrence only further frustrate and arouse the horse, exacerbating the predisposition to stereotypy

and other handling difficulties, and owners should be strongly discouraged from employing such an approach.

The traditional approach is to attempt physical prevention of the stereotypy using things such as anti-weave grilles, anti-cribbing collars, and surgery; these techniques are no longer considered appropriate. Anti-weave grilles are usually ineffective, the horse merely taking a step backwards and continuing to weave. There is also evidence that this increases the frequency of weaving,[51] and a second stereotypy such as head-twisting may develop instead. Devices such as cradles and various bibs and muzzles may however be of some use in the short term for activities such as self-mutilation, where the continuation of the stereotypy puts the horse at unacceptable risk, although these will increase the time required for appropriate husbandry change to be effective.

The anti-cribbing collar incorporating a hinged, curved metallic Y-shaped plate can be effective when fitted correctly, i.e., loose enough to hang loosely against the ears and neck when the horse has his head down, as when grazing, but tight enough to prevent slippage down the neck when the head is raised. It is the size and degree of curvature of the Y-plate that is critical here. It should sit snugly and smoothly against the skin, allowing normal swallowing, only coming into action to constrict the ventral neck muscles when the horse is trying to crib-bite. Simple leather straps or those with spikes are not effective and if tightened in an attempt to improve effectiveness are only likely to injure the horse.

This *post-motivational* blockade is, like the weaving grille, likely to be extremely frustrating for the horse and as such detrimental to welfare. In the setting of imminent euthanasia should crib-biting continue, however, this device could be used to avert the crisis. It is also a less-traumatic option than surgery and has the added advantage of being non-permanent. An anti-cribbing strap should not, however, be left as a long-term solution as with increasing frustration the horse will become more aggressive, difficult to handle, and may well develop another stereotypy. Furthermore, if used as an adjunct to husbandry change, the increased frustration caused by this device will considerably prolong the time taken for elimination of crib-biting attempts.

A thorough review concluded that the surgical approach to crib-biting involving various myectomy and neurectomy techniques was not effective in the long term.[44] Even short-term success cannot be guaranteed, with a number of studies citing success rates ranging from zero to 80%.[44,69–72] Some of those quoting higher success rates, however, comment that the horses continued to crib-bite when stressed or while feeding.

Even if successful, surgery, like the other methods of physical prevention, merely disables the horse to an extent that he cannot display the symptoms of the underlying stressors and physiological changes leading to stereotypic behavior such as crib-biting and is therefore considered detrimental to welfare and should no longer be offered as a treatment option.

Owners requesting surgery to try to eliminate crib-biting should be strongly encouraged to use a correctly fitted anti-cribbing collar for a trial period instead (ideally at least 6 months). In the short-term, this should avert the immediate crisis by stopping crib-biting and provide an opportunity to instigate the recommended husbandry change, before re-evaluating therapeutic options.

NON-STEREOTYPICAL BEHAVIORAL ABNORMALITIES

Coprophagia

Coprophagia describes the ingestion of feces that in the adult horse is a sign of nutritional deficiency. Horses receiving all of their nutrient requirements in the correct balance will avoid eating feedstuffs of pastures contaminated with or close to fecal material.[73] This is an aspect of normal behavior that would generally improve chances of survival by minimizing parasite load. Owners may be concerned that their horse is ingesting parasites, many find this behavior esthetically offensive, and worry that coprophagia will increase the risk of cross-infection from fecal pathogens.

Equine feces do however contain approximately 40–60% total digestible nutrients, with 8–10% crude protein, many trace minerals, particularly calcium and phosphorus and a viable inoculum of intestinal microflora,[5] and so in certain situations the ingestion of feces can be a survival–enhancing activity. For example, coprophagia has been induced by starvation and appeared within 7–10 days in horses fed experimental diets specifically deficient in protein

(containing only 6.2% CP)[74] and roughage (eg less than 1% live weight per day).[55,75] Coprophagia was eliminated by the addition of dietary fiber (in the form of wood-shavings that were consumed preferentially to the feces) and increasing the protein content of the diet to 10% CP, meeting nutritional requirements. Coprophagia has also been reported to occur immediately after sudden dietary change, gradually reducing over a 3–6-week period thereafter.[76] Such a response could also be an evolutionary stable strategy, facilitating gradual microflora repopulation during adaptation to the new diet.

Fecal material also contains vitamin K (in the form of menaquinones synthesized by intestinal bacteria).[48] This may become a valuable source, particularly when the usual dietary source (in the form of phylloquinones abundant in fresh leafy green material) is limited.[5] Although minimal dietary requirements for vitamin K have not been determined for the horse due to the relative abundance of this in traditional horse diets,[48] it has been suggested that many modern husbandry practices are likely to decrease the availability of or increase the requirements for vitamin K in horses, as has been found to occur in other species such as the pig.[5] Thus coprophagy, particularly if seen in association with a reduced blood-clotting time, may be a sign of vitamin K deficiency.

Coprophagy is normal in foals.[77] It is expected to be seen at 1–8-weeks old, the incidence gradually declining with age. The foal consumes fresh feces, predominately that of its own dam. This is thought to be a mechanism for inoculation of the cecum with the microflora required to digest grass, and it has also been suggested that the fresh material is less likely to contain parasites at an infective stage of their life cycle.[77]

Coprophagia can be eliminated by correcting the diet so that all nutritional requirements are met. Particular attention should be given to protein and fiber, and the addition of fresh green material or good-quality green leafy hay along with a trace mineral supplement may be helpful. Total dietary provision of trace minerals and vitamins should be carefully assessed in order to avoid toxic levels of any particular element.[48] Sudden dietary change should be avoided, taking at least 10 and ideally 14 days to gradually replace the old diet with the new. Owners should be reminded that the requirements of growing or older horses (16 plus) may be higher than others. Where group feeding is practiced, and coprophagia seen in only some, the horses should be carefully observed to ensure that competition or bullying is not preventing the horse from attaining his share of the daily ration.

Wood-chewing

The environmental damage caused by wood-chewing is the most common reason for owner concern, although minor oral lesions from splinters may be seen and it is possible that rotting logs, chemically treated timber, or certain species of trees and bushes may contain toxins.

Care should be taken to differentiate between the various behavior patterns that are commonly described as wood-chewing. For example, horses have been seen to strip rings of bark from living trees or bushes to selectively eat leaves with accompanying ingestion of woody stalks of small twigs or to choose to shred and eat dead timber even when lush pasture is available. Alternatively, the damage caused by crib-biting on relatively soft or friable wooden doors, ledges, gates, or fence posts may be mistakenly ascribed to wood-chewing. The horse may scrape and bite wooden doors when excited and frustrated. He may scrape, lick, and chew wooden surfaces or objects when being groomed or has scratched himself. In this case, the damage is usually seen higher than sternum height, often at approximately withers height.

Bark stripping, especially of young trees in the springtime, appears to be a learned activity, with the reward likely to be the sweet taste from sap. Selective ingestion of leaves might similarly be an acquired taste, and it is popularly suggested that this activity may also represent *nutritional wisdom,* the horse requiring specific alkaloids or other elements found in the leaves, although there is no scientific evidence for this. The casual observation that it is primarily the young and older horses that are seen to do this within a mixed group is often mentioned in support of this idea. Alternatively, these activities may be a form of pica.

Wood-chewing seen only while being groomed is a form of re-directed mutual grooming. The horse may also attempt to bite and nibble the handler, lead-rope or any other object within reach here, resorting to a wooden surface when these are not available or when the handler moves out of reach.

Generally however, wood-chewing describes the selective ingestion of dead wood. Rates and amounts

of material consumed vary considerably between individuals. In one study, a pony was reported to eat as much as 2 lbs of wood from a stable partition per day without suffering deleterious consequences.[78]

The owner may consider this sort of damage to be a vice, representing deliberate destructiveness, or may be particularly concerned when dead wood is eaten in apparent preference to lush pasture.

Boredom is frequently suggested as a reason for wood-chewing, particularly when this is seen where other more-nutritious food appears to be readily available. However, as for coprophagy and some stereotypes, experimental work has shown that there are some more specific causal factors.

A number of studies have found that lack of roughage in the diet is a major contributory factor in wood-chewing.[18,74,75,78,79] The horse has a very high requirement for roughage in order to maintain hind-gut function and improve digestive efficiency. A diet high in concentrates or lush pastures with a high proportion of relatively young, less-fibrous grasses in comparison to more mature or varied pastures may not provide enough fiber, although meeting other dietary requirements. In this case, selective ingestion of a highly fibrous material such as wood, like coprophagy, may represent a survival enhancing response to specific dietary deficiency.

Access to a paddock was found to be associated with an increased risk of wood-chewing.[14] This may simply reflect increased opportunity regarding access to wood, although it is possible that associated dietary changes, such as reducing the forage ration allowing for nutrients provided from the paddock particularly if this was relatively lush pasture, might have reduced fiber intake.[80]

Alternatively, these horses may have been colder than others kept stabled, as it has been reported that horses are more likely to chew wood in cold, wet weather.[81] This has been suggested to be due to an attempt to increase body temperature by increasing the heat produced by hind-gut fermentation associated with increased digestible fiber intake.[81] However, the wood comprising this extra fiber is not digested in the horse[82] and so will not increase temperature in this way. Cold, wet weather may, however, predominate at certain times of the year in association with changes in pasture composition that may affect wood-chewing as already described. Alternatively, improved digestive efficiency achieved by increased rate of passage associated with increased fiber intake is an evolutionarily stable strategy in the horse that could also explain this finding.

One review excluded the possibility of other specific nutrient deficiency as a cause of wood-chewing,[81] although it has subsequently been suggested that many typical modern horse diets may be deficient in certain trace elements available from wood. These include substances such as cadmium, chromium, molybdenum, vanadium, and tin and perhaps other essential mineral elements yet be discovered.[5] For example, incidental ingestion from soil or weeds while grazing sparse, relatively uncultivated pasture may have provided sufficient amounts of such minerals that may not be available in hay obtained from relatively lush, cultivated pasture. Similarly, highly processed concentrate feedstuffs made from various agricultural by-products, which are low in indigestible fiber and to which the various trace element minerals currently known to be required by the horse must be added separately, may not adequately provide for all of the horses' needs.[5]

Limited social contact has also been found in association with an increased incidence of wood-chewing,[14] and one study suggested that the wood-chewing seen in two ponies that chewed through the partition separating them until they could put their heads through may have done so to increase their contact.[78] This study found that increased exercise did not affect the amount of wood-chewing seen, although another study[83] did report a beneficial effect of exercise. It is possible that the exercise in the latter study also increased social contact, offering an explanation for these conflicting results.

For some forms of wood-chewing, owner concern can be ameliorated by a number of practical husbandry changes limiting the environmental damage. For example, valuable or potentially toxic trees and bushes should be securely fenced off well out of the reach of horses and pruned as required. The damage caused by redirected mutual grooming can by prevented by tying the horse out of reach of wooden surfaces. Where this is not practicable, a comforter similar to that recommended for crib-biting horses but standing at approximately withers height can be used. The horse will be most likely to redirect his biting and nibbling activity to this if it is placed beside the shoulders. Reducing general levels of frustration

as described for stereotypic behavior will help to reduce the incidence of door-scraping with the teeth.

Where horses are selectively consuming dead wood, the most effective therapy is to increase the amount of fiber in the diet, and it is recommended that horses are always fed at least 1% of live weight in the form of highly fibrous roughage.[48] Smearing surfaces with unpalatable substances is generally not effective.[81] Increasing social contact is also likely to be beneficial to reduce wood-chewing,[18,78,81] as may a general trace element feed supplement or mineralized salt lick.[5] The addition of sodium bicarbonate to the diet reduced wood-chewing in one experimental study,[75] and so feedstuffs likely to reduce cecal pH should be avoided.

Pica

Coprophagia and wood-chewing are often colloquially described along with the eating of other apparently non-nutritional substances such as soil or stones as *depraved appetite* or pica. This sort of activity is usually associated with specific dietary deficiencies, particularly of trace minerals. The diet for any horse exhibiting pica should be carefully checked to ensure that there are adequate amounts and the appropriate relative balance of trace minerals, particularly calcium and phosphorus. Pasture plants can grow well without some of the trace mineral elements essential for animals. For example, of the 14 trace elements known to be essential for the horse (calcium, phosphorus, magnesium, sulphur, sodium, chlorine, iron, iodine, manganese, cobalt, selenium and zinc), selenium, iodine, sodium, and cobalt are rarely needed by plants, and so an apparently lush pasture may be deficient in these elements.[5] In areas with acidic soil and a relatively high rainfall, these mineral elements are less likely to be taken up into pasture plants, and there may be localized soil and herbage deficiencies affecting one field on a particular farm, but not another. Hence, pica may only be seen when horses are grazing particular areas. Forages are particularly variable in trace mineral content, and a change of hay even just to that made from a different field or cut may be associated with pica. The relative balance of mineral elements affects overall availability of each, and horses are less tolerant of variation here at various stages of life. Thus, pica may be seen only in younger, growing horses, for example, from a mixed group grazing together and being fed in the same way. Many owners are aware of the need for adequate calcium in young horses and during gestation. Calcium supplementation, if given in excess can decrease the availability of other minerals such as phosphorus, magnesium, zinc, manganese, copper, iodine, and iron and so deficiency and pica may ensue. Although horses have not been found to have specific appetites for minerals such as calcium and phosphorus for example, appetite for salt (NaCl) varies with requirements,[5] and pica may represent an attempt to correct for a dietary lack. Feral ponies have been seen to seek out and selectively consume soil from specific sites, returning repeatedly to the same site to do so. This is traditionally regarded as an instinctive method of correcting dietary deficiencies.

In the foal, specific deficiencies in copper and zinc have been associated with regular consumption of dirt and stones.[76] Furthermore, the range between minimum and maximum tolerable Ca:P ratio is much less in the foal than in older horses (e.g., 1.2:1–1.5:1 for foals compared to 1:1–5:1 in the mature horse); thus, relatively slight dietary changes here are much more likely to affect foals than older horses. Mare's milk has been shown to be deficient in iron and copper.[5] Pica in the foal may also be coincidental to investigative behavior or redirected suckling, particularly if suckling time is limited as for example when hand-reared or when there are difficulties with maternal acceptance.

A thorough analysis of dietary content and trace mineral status of the affected horse may be impracticable and is likely to be expensive, and so a blanket approach to therapy is recommended in the first instance. A balanced trace mineral supplement should be chosen and given regularly, with a self-feed mineralized salt-lick available at all times. Owners should be discouraged from giving additional feed supplements or mineral sources to avoid complication from mineral availability interactions. Different hay or forage sources should be tried and grazing on mature and varied pasture offered where possible. In the foal a well-balanced, palatable, and accessible creep-feed containing enough iron and copper should be made available from the second week of life. Liming pastures, particularly where organic fertilizers such as horse manure have been used over a number of years, will decrease acidity and allow greater uptake of mineral

elements from the soil into herbage. It is colloquially reported that a handful of soil from the pasture or soil-lick placed in the water supply for each horse has been found to eliminate pica. The minerals lacking in herbage may leach from the soil and be available in the solution, and traditional husbandry practices such as feeding hay from a different area when grazing a particular pasture may also help to cover local mineral deficiencies.

Should these general husbandry changes prove to be unsuccessful, a detailed diagnostic analysis may be required to locate any specific nutritional deficiency, particularly of calcium, phosphorus, iron, copper, zinc, cobalt, iodine, and selenium.

Hay-Dipping

Some horses habitually dip or dunk mouthfuls of hay into their drinking water before fully chewing and swallowing the hay. This is carried out in a repetitive and predictable pattern that initially appears to be stereotypic. The water source fills with leaching hay and automatic drinking bowls may become blocked. Where the water is at a distance from the hay, a horse persisting with this activity can cause a lot of waste and spillage. It is usually the resulting mess that is the main concern of the owner.

Although hay-dipping in many ways resembles a stereotypy, it has been shown to be a learned behavior problem.[84, 85] These horses have acquired a taste preference for the more succulent dipped hay, probably by operant conditioning after accidentally dipping as when drinking soon after taking a mouthful of hay. In a study of two horses that routinely dipped their hay, it was found that they did not show a preference for water in which hay had previously been soaked (which would have acquired a distinctive and sweet taste from nutrients leaching out of the hay).[84] Neither did they consume more water when dipping hay nor did they drink less to compensate for that consumed when eating; so, this hay-dipping was not a form of polydipsia.

Some horses will stop hay-dipping if the water source is removed sufficiently far from the hay source, although others will persist. This behavior can best be extinguished by feeding already soaked hay (i.e., hay that has been completely immersed for at least 30 min).[84] The horse initially continues to dip the soaked hay, but as there is no longer any reward in doing this (i.e., the hay does not become any more succulent), the horse is less likely to repeat this activity, and it gradually ceases altogether. The time required for complete elimination depends on the initial frequency of dipping, usually taking 10–14 days.

Door-Banging and Stall-Kicking

Some stabled horses persist in kicking the walls or banging their knee, fetlock, or hoof against the door. This can be carried out repeatedly and to the extent of causing such traumatic injuries as phalangeal fractures, splint fractures, calcaneal bursitis (capped hock), or plantar desmitis. Apart from these obvious injuries or other minor lesions requiring veterinary attention, owners may be very concerned about the resulting environmental damage and/or the accompanying noise. This may also be given as a reason for some livery yards for refusing to keep these horses, and the anxious owner may wish urgent assistance in stopping this disruptive behavior.[86]

This behavior may, like hay-dipping, initially appear stereotypic. For example, the actions are repetitive and are generally seen when the horse is aroused and frustrated, particularly when anticipating feed arrival or when other horses are being moved nearby. Unlike stereotypes, however, door-banging and stall-kicking are also seen when the horse is quiet and alone, and the owner may consider he is probably bored.

Careful observation is required to elucidate the exact cues for starting and stopping a bout of kicking and also to differentiate this learned behavior from inadvertent kicking that may cause similar traumatic injuries occurring, for example, when the horse experiences difficulty in lying down or rising safely, which may arise from other injuries or disorders, a small stable, lack of bedding or slippery floor. For example, most horses lie down at least twice a day, for a short time, assuming primarily sternal recumbency around midday, usually between 12:00–14:00, and for a longer period including lateral recumbency, usually between 00:00–04:00. Where kicking occurs predominately at these times, difficulty in lying and rising should be suspected. As the yard or barn may also be quiet at these times of day and associated kicking may also be attention seeking behavior, direct observation is required to confirm these suspicions and the primary cause investigated. Alternatively, this behavior may result from self-defense or aggression directed towards a neighboring horse

or may a sign of acute frustration or social isolation stress, and care should be taken to ensure that the affected horse has sufficient feed, physical comfort, and a suitable companion or is at least able to see other horses at all times.

In the absence of obvious causes of frustration, door-banging and stall-kicking are predominant examples of attention seeking behavior that can develop into a learned behavior problem in the horse. The noise produced (which is likely to be perceived before any resulting pain) and the attention elicited reward these activities. Even an angry yell or a well-aimed dandy brush constitutes a reward from the horse's point of view. The owner may mistakenly feel that he has successfully punished the horse, as the horse may stop for a short time after achieving his goal by gaining the desired attention and reaction from the owner.

For the otherwise well-provided for horse, a radio left on is often enough to eliminate attention seeking, stall-kicking, or door-banging. A station broadcasting a mixture of talk and a variety of music seems to be most effective here, although owner preferences usually take precedence.

Where this is not successful, a retraining program of extinction and/or counter-conditioning is required. During retraining, padding the door (e.g., with coconut matting, old carpet, or rubber mats) or replacing this with a single breast bar and using protective boots or stable bandages will all help remove the reward, reduce the risk of injury to the horse, and may also reduce environmental damage.

Where the kicking or door-banging occurs in response to specific cues, such as vehicles arriving, elements of feed preparation and so on, it will be very helpful for the owners to expose the horse as often as practicable to these cues without their usual consequences. This approach has many practical difficulties, and the horse may will learn to respond to new cues as routines change. The more strict a daily routine is, the more likely a horse is to learn the appropriate cues and to respond with frustration-related kicking to cues further in advance of the expected reward, e.g., food.

Where specific cues cannot be identified or the above approach is impractical or unsuccessful, a program of extinction can be used to eliminate door-banging and kicking. Everyone involved should be instructed to completely and for evermore ignore the horse during and immediately after the kicking episodes. This must be maintained and includes even looking towards the horse at these times. He should be given attention only after a period of standing quietly. Initially, this can be done only after 10–20 sec of standing still, and the time required gradually extended. The reward should consist initially of a look in his direction, followed by a call or a few words, followed by approach and a pat or treat. The final part of the reward sequence can be left out occasionally. If the horse begins to kick again during the reward sequence, it should be immediately aborted and the horse ignored. It is particularly important that the horse is never again rewarded with attention for kicking. Wearing earmuffs or a personal stereo will help the owner to comply with instructions to ignore the horse. Should patience be lost and the owner eventually respond to the horse after a prolonged bout of kicking or at the end of a stressful day, he will be inadvertently training the horse to kick harder for longer, having put him on a relatively higher variable ratio schedule of reinforcement. Effective punishment can be very difficult to achieve, and there is always the risk that inaccurate timing or an inappropriate technique will result in the horse simply learning that the owner inflicts pain or discomfort and developing a more dangerous defense aggression problem.[87] For these practical and other ethical reasons, owners should be dissuaded from attempting to retrain horses by punishment. The most effective long-term solution to this behavior problem is to continue to completely ignore the horse when kicking and to reward him for standing quietly for gradually increasing lengths of time.

REFERENCES

1. Holmes G. 1839. On Crib-biting. *Proc Vet Med Assoc* 167–80.
2. Kiley-Worthington M, Wood-Gush DGM. 1987. Stereotypic behavior in stabled horses. *Equine Vet Sci* 6:49–54.
3. Mason G. 1991. Stereotypes: a critical review. *Anim Behav* 41:1015–37.
4. Lawrence AB, Rushen J. 1993. Stereotypic animal behavior—fundamentals and application to welfare. CAB International, Oxon.
5. Cunha TJ. 1991. *Horse feeding and nutrition*, London:Academic Press.
6. Houpt KA. 1991. Domestic animal behavior for veterinarians and animal scientists. New York: Cornell Univ Press.

7. Bennet D. 1992. "The evolution of the horse". In *Horse Breeding and Management*, edited by Evans WJ, 1–40. Philadelphia:Elsevier.
8. Jarvis C. 1976. The evolutionary strategy of the equidae and the origins of rumen and cecal digestion. *Evolution* 30:757–74.
9. Hickman J. 1987. *Horse Management*. London: Academic Press.
10. Hughes BO, Duncan IJH. 1988. The notion of ethological 'needs', models of motivation and animal welfare. *Anim Behav* 36:1696–707.
11. McGreevy PD, Richardson JD, Nicol CJ, *et al*. 1995. Radiographic and endoscopic study of horses performing on oral based stereotypy. *Equine Vet J* 27:92–5.
12. Lane JG. 1993. Fourth branchial arch defects in the horse a report of 20 cases. *Proc Bain Fallon Memorial Lectures*. Australian Equine Veterinary Association 15:215–32.
13. Prince D. 1987. *Behavior problems in horses*, edited by McBane S. London:David & Charles.
14. Luescher A, McKeown DB, Dean H. 1996. A cross-sectional study on compulsive behavior (stable vices) in horses. Proc Int Cong Equine Clinical Behavior.
15. Hodosa T. 1950. On the heritability of susceptibility to wind-sucking in horses. *Jap J Zoo Tech Sci* 21:25–8. (kindly translated by S Sato of Miyazaki University).
16. Vecchiotti G, Galanti R. 1985. Evidence of heritability of cribbing, weaving and stall-walking in Thoroughbred horses. *Livestock Prod Sci* 14:91–5.
17. Kiley-Worthington M. 1983. Stereotypes in horses. *Equine Practice* 5:34–40.
18. Henderson J. 1994. The inheritance of susceptibility to stereotypic behavior patterns in the horse. UFAW vacation scholarship (unpublished observation).
19. McGreevy PD, Cripps PJ, French NP, *et al*. 1995. Management factors associated with stereotypic and redirected behavior in the thoroughbred horse. *Equine Vet J* 27:86–91.
20. Miller-Baker AE, Crawford BH. 1986. Observational learning in horses. *App Anim Behav Sci* 15:7–13.
21. Mal ME, Friend TH, Lay DC, *et al*. 1991. *App Anim Behav Sci* 31:13–24.
22. Bagshaw CS, Ralston SL, Fischer H. 1994. Effects of orally administered tryptophan on acute isolation stress in the horse. *App Anim Behav Sci* 40:1–12.
23. Marsden MD. 1995. On the inheritance of susceptibility to stereotypic behavior (stable vices) in Przewalski's horses. Proc Int Cong Gen Dis Horse. SVA, Interlaken.
24. Breen M, Downs P, Irvin Z, *et al*. 1994. Intragenic amplification of horse microsatellite markers with emphasis on the Przewalski's horse. *Anim Genetics* 25:401–5.
25. Baker H, Joh TH, Reis DJ. 1980. Genetic control of number of mid-brain dopaminergic neurones in inbred strains of mice: relationship to size and neuronal density of the striatum. *Proc Natl Acad Sci USA* 77:4369–73.
26. Fink JS, Reis DJ. 1981. Genetic variations in midbrain dopamine cell number: parallel with differences in responses to dopaminergic agonists and in naturalistic behaviors mediated by central dopaminergic systems. *Brain Res* 222: 335–49.
27. Randall PK, Randall JS. 1986. Mouse strain differences in apomorphine induced behavior: an empirical and methodological study. *Neurosci* 100:85–92.
28. Shannon HE, Bemis KG, Peters SC. 1991. Potency and efficacy of dopamine agonists in mouse strains differing in dopamine cell and receptor number. *Pharmacol Biochem and Behav* 40:103–7.
29. Cabib S. 1993. "Neurobiological basis of Stereotypes". In *Stereotypes fundamentals and application to welfare,* edited by Lawrence AB, Rushen J, 119–45. Oxon:CAB International.
30. Trabucci M, Spano PF, Racagini G, *et al*. 1976. Genotype dependent sensitivity to morphine–dopamine involvement in morphine-induced running in the mouse. *Brain Research* 114:536–40.
31. Racagini G, Bruno F, Juliano E, *et al*. 1979. Differential sensitivity to morphine-induced analgesia and motoractivity in two inbred strains of mice: behavioral and biochemical correlations. *J Pharmacol Exp Therap* 209:111–6.
32. Katz KJ, Doyle RL. 1980. Enhanced responses to opiates produced by a single gene substitution in the mouse. *Eur J Pharmacol* 67:301–3.
33. Puglisi-Allegra S, Oliverio A. 1990. *Psychobiology of stress*, edited by Pulisi-Allegra S, Oliverio A. Dordrecht:Kluwer Academic Press.
34. Kusunose R. 1992. Diurnal pattern of cribbing in stabled horses. *Jpn J Eq Sci* 3:173–6.
35. Hamra JG, Kammerling SG, Wolfsheimer KJ, *et al*. 1993. Diurnal variation in immuno-reactive β-endorphin levels and experimental pain thresholds in the horse. *Life Sci* 53:121–9.
36. Gillham SB, Dodman NH, Shuster L, *et al*. 1994. The effect of diet on cribbing behavior and plasma β-endorphin in horses. *App Anim Behav Sci* 41: 147–53.

37. Canali E, Ferrante V, Mattiello S, *et al*. 1996. Plasma levels of β-endorphin and *in vitro* lymphocyte proliferation as indicators of welfare in horses in normal or restrained conditions. *Pferdheilkunde* 12:415–8.
38. Pilkington J. 1993. Periodicity and factors affecting the performance of Stereotypes in stabled horses. BSc thesis, Dept Zoology, University of Edinburgh.
39. Shannon HE, Bemis KG, Perrs SC. 1991. Potency and efficacy of dopamine agonists in mouse strains differing in dopamine cell and receptor number. *Pharmacol Biol Behav* 40:103–7.
40. Stoessl AJ. 1994. Dopamine D1 receptor agonist-induced grooming is blocked by the opioid receptor antagonist naloxone. *Eur J Pharmacol* 259: 301–3.
41. Breathnach B, Murphy M. 1988. The effect of a narcotic antagonist (diprenorphine) in the treatment of a stereotypic behavior pattern (box walking) in the equine. UFAW vacation scholarship report.
42. Dodman NH, Shuster L. 1988. Use of a narcotic antagonist (nalmefene) to suppress self-mutilation behavior in a stallion. *J Amer Vet Med Assoc* 192:1585–7.
43. Dodman NH, Shuster L, Court M, *et al*. 1987. Investigation into the use of narcotic antagonists in the treatment of a stereotypic behavior pattern (crib-biting) in the horse. *Am J Vet Res* 48: 311–9.
44. Owen Rh sp Rh. 1982. Crib-biting and windsucking, that equine enigma. *The Vet Ann* 12:159–67.
45. Luescher UA, McKeown A, Halip J. 1991. Reviewing the causes of obsessive-compulsive disorder in horses. *Vet Med* 86:527–30.
46. Marsden MD. 1993. Feeding practices have greater effect than housing practices on the behavior of housed horses. *Proc 4th Int Livestock Symp,* 314–8.
47. Wurtman RJ, Heftl F, Melamed E. 1981. Precursor control of neurotransmitter synthesis. *Pharmacol Rev* 32:315–35.
48. National Research Council. 1989. Nutrient requirements of horses. Washington D.C.:National Academy Press.
49. Oltras CM, Mora F, Vives F. 1987. β-endorphin and ACTH in plasma: effects of physical and psychological stress. *Life Sci* 40:1683–6.
50. Ellinwood Jr. EH, Kilby MM. 1975. Amphetamine stereotypy: the influence of environmental factors and prepotent behavioral patterns on its topography and development. *Biol Psychiatry* 10:3–16.
51. McBride SD. 1996. Comparison of physical and pharmacological prevention of stereotypic behavior in the horse. *Proc Int Cong Equine Clinical Behavior*.
52. Lebelt D. 1996. Physiological correlates in association with cribbing behavior in horses. *Proc Int Cong Equine Clinical Behavior.*
52. Lebelt D. 1996. Physiological correlates of cribbiting behavior in horses. Dissertation Med-Vet, Univ of Munich, Germany.
53. Manfredi B, Sacerdote P, Velic-Rudolvic J, *et al*. 1993. Evidence for an opioid inhibitory effect on T-cell proliferation. *J Neuroimmunol* 44:43–8.
54. Capper SR. 1992. The effect of feed-types on ingestive behavior in different horse types. BSc (Hons) thesis, Univ of Edinburgh.
55. Nagata Y. 1971. Effects of various degrees of size and hardness of complete pelleted food on feeding behavior of horses. *Exp Report Eq Health Lab* 8:72.
56. Meyer HV, Ahlsvede L, Reinhard HJ. 1975. Duration of feeding, frequency of chewing and physical form of feed for horses. *Deutsche Tierartzliche Wachenschrift* 82:54–8.
57. Houpt KA. 1982. Oral vices of horses. *Eq Pract* 4:16–25.
58. Henderson J. 1995. Investigation of the use of a 'food ball' in prevention of stereotypy in the horse. MSc thesis, Univ of Edinburgh.
59. Feh C, de Mazieres J. 1993. Grooming at a preferred site reduces heart rate in horses. *Anim Behav* 46:1191–4.
60. McCarthy RN, Jeffcott LB, Funder JW, *et al*. 1991. Plasma β endorphin and adrenocorticotrophin in young horses in training. *Austr Vet J* 68:359–61.
61. MacCormack JAD, Bruce JM. 1991. The horse in winter—shelter and feeding. *Farm Buildings Progress* 105:10–3.
62. Dodman NH, Shuster L. 1994. Pharmacological approaches to managing behavior problems in small animals. *Vet Med* 89:960–9.
63. Houpt KA, McDonnell SM. 1993. Equine Stereotypes. *Compend Cont Educ Equine Prac* 15:1265–72.
64. Leonard BE. 1992. Fundamentals of Psychopharmacology. Chichester:John Wiley and Sons.
65. Kamerling SG, Hamra JG, Bagwell CA. 1990. Naloxone induced abdominal distress in the horse. *Equine Vet J* 22:241–3.
66. Cronin GM, Wiepkema PR, van Ree JM. 1986. Endorphins implicated in stereotypes of tethered sows. *Experientia* 42:198–9.
67. McDonnell SM. 1996. Pharmacological aids to behavior modification in horses. *Proc Int Cong Equine Clinical Behavior.*
68. McClure SR, Chaffin MK, Beaver BB. 1992. Non-pharmacological management of stereotypic

self-mutilation in a stallion. *J Amer Vet Med Assoc* 200:1975–7.
69. Greet TRC. 1982. Windsucking treated by myectomy and neurectomy. *Equine Vet J* 14: 299–301.
70. Turner AS, White N, Ismay J. 1984. Modified Forssell's operation for crib-biting in the horse. *J Amer Vet Med Assoc* 184:309–12.
71. Fjeldborg J. 1996. Evaluation of two different surgical techniques in the treatment of cribbing. *Proc Int Cong Equine Clinical Behavior*.
72. Ritzberger-Matter G, Kaegi B. 1996. Retrospective analysis of the success rate of surgical treatment of aerophagia in horses. *Proc Int Cong Equine Clinical Behavior*.
73. Odberg FD, Francis-Smith K. 1977. Studies on the formation of ungrazed elimination areas in fields used by horses. *App Anim Ethol* 3:27–34.
74. Schurg WA, Frei DC, Cheke PR. 1977. Utilization of whole corn plants by horses and rabbits. *J Anim Sci* 45:1317.
75. Willard JG, Willard JC, Wolfram SA, *et al*. 1977. Effect of diet on cecal pH and feeding behavior of horses. *J Anim Sci* 45:87–93.
76. Ralston SL. 1986. Feeding behavior. *Vet Clinics North America Equine Pract* 2:609–21.
77. Crowell-Davies SL, Houpt KA. 1985. Coprophagy by foals: effects of age and possible functions. *Equine Vet J* 17:17–9.
78. Houpt KA. 1986. Stable-vices and trailer problems. *Vet Clinics of North America Equine Pract* 2:623–34.
79. Haenlein GFW, Holden RD, Yuon J. 1966. Comparative responses of horses and sheep to different physical forms of alfalfa hay. *J Anim Sci* 25:740–3.
80. Ralston SL, van der Broek G, Bailie CA. 1982. Feed intake patterns and associated blood glucose free fatty acid and insulin changes in ponies. *J Anim Sci* 49:838–47.
81. McCall CA. 1993. Wood-chewing by horses. *Eq Pract* 15:35–6.
82. Laut JE, Houpt KA, Hintz HF, *et al*. 1985. The effects of caloric dilution on meal patterns and feed intake of ponies. *Physiol Behav* 35: 549–54.
83. Krzak WE, Gonyou HW, Lawrence LM. 1991. Wood-chewing by stabled horses: diurnal pattern and effects of exercise. *J Anim Sci* 69:1053–8.
84. Marsden MD. 1993. Are changes in time-budgeting indicative of changes in welfare? Proc Brit Soc Anim Prot. Scarborough, *Anim Prod* 56, 15–17.
85. Waring GH. 1983. *Horse Behavior.* New Jersey: Noyes Publications.
86. Crowell-Davies SL, Houpt KA. 1986. *Vet clinics of North America Equine practice- Behavior,* Philadelphia:Saunders.
87. Marsden MD. 2005. *How Horses Learn*, London: J A Allen.

30
Miscellaneous Conditions

Martin Furr

CHOLESTEROL GRANULOMA

Cholesterol granulomas are circumscribed, smooth, firm masses found within the choroid plexus of up to 20% of older horses.[1] They are also referred to as cholesteatomas or cholesterinic granulomas. Histologically, most masses are composed of cholesterol crystals in a bed of granulation tissue without epithelial elements.[2] The masses appear to be more frequent in the fourth ventricle than in the lateral ventricles; however, it has been stated that the granulomas in the lateral ventricle seem more likely to cause clinical disease. The etiology and mechanism of formation for cholesterol granulomas remains unclear, but they are likely to be the result of a granulomatous reaction to cholesterol crystals in the choroid plexus.

Although most of these benign masses remain clinically silent, they can grow to such a size that they result in clinical illness. This occurs either by obstruction of cerebrospinal fluid (CSF) with secondary hydrocephalus or by direct compression of nervous tissue (Figure 30.1). Most reported cases have been seen in middle-aged horses (10–15 years old), and various clinical signs referable to cerebral disease have been reported. Specific signs include depression, reluctance to move forward, stiff gait, seizures, blindness, and circling.[2–4] Clinical signs may be intermittent or consistent once noted.

Serum chemistry and complete blood cell count in reported cases are usually normal and do not demonstrate any consistent pattern of abnormality. CSF evaluation usually reveals fluid that is mildly xanthochromic and with normal or mildly increased total protein concentrations.[2,3] A mild pleocytosis (i.e., 25–30 nucleated cells/μl CSF) has been reported in some cases. In one case, the monocytes were vacuolated and contained phagocytized basophilic granular material, which were later considered to be phagocytized fragments of the granuloma.[2]

Antemortem diagnosis has not been reported, but the emerging use of computerized tomography (CT) or magnetic resonance imaging (MRI) scans should make this possible. No specific treatment exists; however, treatment with steroids, nonsteroidal anti-inflammatory and antiedema drugs often provides transient improvement. Diagnosis is made usually on postmortem, while the characteristic large, smooth, pearly, and granular mass is noted within the fourth or lateral ventricles.

INTRACAROTID INJECTION

Inadvertent intracarotid injection occurs occasionally in the horse during attempted intravenous injections. The clinical event that follows is variable in its severity and depends upon the nature of the compound injected and the volume. One author report twenty-four cases of intracarotid injection, in which there were five fatalities.[5] It was also reported that individual animals had varying responses to intracarotid injection of the same drug.[5] Although this suggests some component of individual animal sensitivity, the variable response might also have arisen from incomplete delivery of the dose due to the method of injection. In most cases, the signs occur within seconds of the intracarotid injection but may be delayed for a few minutes. Signs can occur abruptly and violently or be preceded by a few moments of progressive anxiety and trembling before collapse and convulsions. Systemic signs such as arrythmias, changes in blood pressure, and

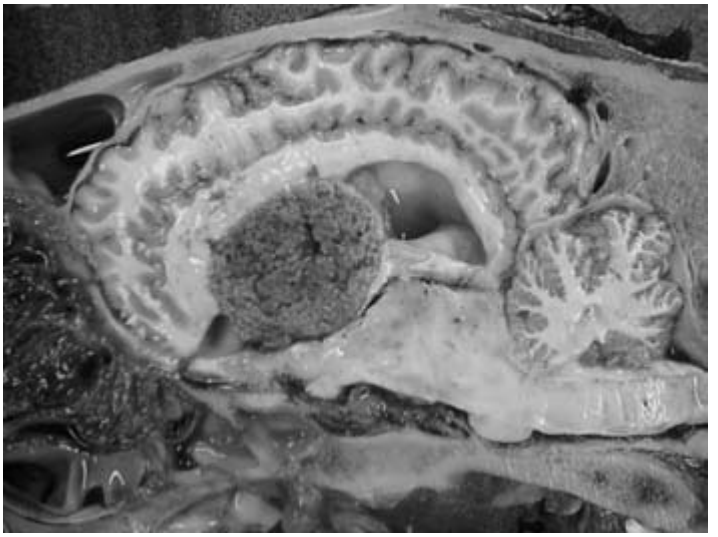


Figure 30.1. Sagittal view of a cholesterol granuloma. Note the internal hydrocephalus present as a result of blockage of flow of cerebrospinal fluid.

"blowing" respiration can be seen. With water soluble compounds such as xylazine, acepromazine, and butorphanol, horses usually regain consciousness within an hour, although full recovery may take up to one week. During this time, clinical abnormalities such as facial hypalgesia, blindness, and mild hemiparesis may be seen. If the injection occurs with viscous or irritant drugs, drug suspensions, or oil-based compounds, then the reaction is more acute and the outcome worse. Seizures, coma, and prolonged recumbency can occur, with euthanasia a common outcome. In an experimental setting, three of five horses given 3.3 ml/800 lb body weight of promazine were euthanized after 20 h of recumbency.[5] Another animal given 50 ml of 20% calcium gluconate solution by intracarotid injection collapsed, convulsed, and then died 6 min after completion of the injection.[5]

Treatment is primarily symptomatic; anticonvulsant medication is appropriate, as is intravenous dimethylsulfoxide (DMSO) or mannitol and dexamethasone. Postmortem examination finds signs of cerebral edema and vascular endothelial damage, with necrosis and vacuolation in subcortical white matter.[5]

Prevention is achieved by careful placement of syringes for intravenous injection. Ideally, an 18-G needle should be used and directed down the vessel (toward the heart). If the carotid artery is entered with an 18-G needle, the blood usually spurts only a few inches, and with a 20-G needle, the blood drips even if it is within the carotid artery. Color of the blood is suggestive but can be misleading. If infusions are needed, placement of an intravenous catheter is advised.

AIR EMBOLISM

The widespread use of intravenous catheters has led to several cases of air embolism, which typically occur when the catheter becomes disconnected and air is aspirated by the catheter. In dogs, a dose of 0.75 ml/kg of air injected into the carotid artery resulted in some deaths and cerebral lesions were found.[6] There is very limited scientific literature on this topic in the horse, however, 4l of room air administered by intravenous injection can result in death.[7] It is often impossible clinically to determine how long the catheter has been disconnected or how much air might have been aspirated.

Clinical signs reflect diffuse cerebral irritation, and horses typically tremble and pace the stall and are anxious; mild ataxia may be seen. In severe cases, horses can become manic, crashing into the stall and falling. Seizures and blindness can be seen. In addition to the neurologic signs, most horses have an elevated heart rate and abnormal respiration.

Treatment is nonspecific, and in mild cases, no specific treatment is required. In more severe cases, the use of corticosteroids, nonsteroidal anti-inflammatory drugs, multi-convulsants, and DMSO

is potentially beneficial. Most horse appear to recover within 1–2 h; however, in severe cases, blindness has persisted for several days.

REFERENCES

1. Sullivan ND. 1985. The nervous system. In *Pathology of Domestic Animals*, edited by Jubb KVF, *et al*., 201–338. Orlando: Academic Press.
2. Johnson PJ, Lin TL, Jennings DP. 1993. Diffuse cerebral encephalopathy associated with hydrocephalus and cholesterinic granulomas in a horse. *J Am Vet Med Assoc* 203:694–7.
3. Jackson CA, deLahunta A, Dykes NL, *et al*. 1994. Neurological manifestation of cholesterinic granulomas in three horses. *Vet Rec* 135:228–30.
4. Duff S. 1994. Cholesterinic granulomas in horses. *Vet Rec* 135:288.
5. Gabel AA, Koestner A. 1963. The effects of intracarotid artery injection of drugs in domestic animals. *J Am Vet Med Assoc* 142:1397–403.
6. Worman LW, Siedel B. 1966. Treatment of cerebral air embolism in the dog. *Am J Surg* 111:820.
7. Gabel A. 1970. Air embolism. *J Am Vet Med Assoc* 156:283.

Index

acepromazine (for stereotypical behavior), 392
acyclovir, 58
albumin quotient, 34
Alzheimers type 2 cells, 264
aminoglycosides, 57
amitraz, 343
amphotericin b, 232
anencephaly, 3
Angiostrongylus cantonensis, 214
anisocoria, 114
antibody index, 51
anticonvulsants, 80
Arboviruses, 177
astrocytes, 48
ataxia, 70, 95
  causes of, 96, 97, 98
  diagnosis, 95
autonomic nervous system, 8
axonopathy, 166
axonotmesis, 329
azithromycin, 57

baclofen, 348, 367
Bacterial meningitis, 187
  agents of, 187
  treatment, 191, 194
Balamuthia mandrillaris, 232
barkers, 357
benztropine, 338
bethanechol hydrochloride (for urinary incontenance), 123
blindness, 114
blood-brain barrier, 33
Borna virus, 175
Borrelia burgdorferi, 233
Botulism, 111, 225
Bouin's solution, 158
box-walking, 378
brain-heart syndrome, 312
brainstem auditory evoked potentials, 109, 135
bromide
  anticonvulsant, 87
  toxicity, 340
Bungners bands
  in stringhalt, 367
  Equine motor neuron disease, 244
Bunyaviridae, 181
butorphanol (in anesthesia), 150

Cache Valley Virus, 181
calcium, 276
calcium versenate, 342
California encephalitis virus, 181
caloric test, 109
cauda equina syndrome, 119
cauda equine neuritis (see polyneuritis equi)
central pattern generator, 365
central pontine myelinolysis, 270
cephalosporins, 56
cerebellum, 25
  abiotrophy, 250
  degeneration, 250
  herniation, 106
  peduncles, 13
cerebral blood flow, 149
cerebral necrosis (postanesthetic), 153
cerebrospinal fluid, 33
  cauda equina, 120
  collection, 34
  composition, 39
  electrophoresis, 286
  formation, 33
  immunoglobulins, 49
  lymphocytes, 48
  traumatic brain injury, 315
cervical vertebral stenotic myelopathy, 283
circling, 379
clomipramine, 392

Clostridium botulinum, 225, 247
Cloward technique, 291
Coastal staggers, 353
coat color dilution lethal syndrome (see lavender foal syndrome)
convulsives, 357
coprophagy, 395
Corticosteroids
  anti-inflammatory, 58
  spinal cord injury, 322
  traumatic brain injury, 107, 319
Cranial nerves, 65
  abducens, 68
  facial, 11, 68, 110, 330
  glossopharyngeal, 68
  hypoglossal, 68, 110
  obturator, 333
  oculomotor, 11, 68
  olfactory, 16
  optic, 15, 68
  testing, 67
  trigeminal, 13, 29, 68
  trochlear, 14, 68
  vagus, 11, 68, 110
crib-biting, 377
Cryptococcus albidus, 231
Cryptococcus laurentii, 231
Cryptococcus neoformans, 231
Cushing's effect, 151
Cushing's reflex, 312
C-value, 51
cystometrography, 123
cytotoxic edema, 308

Dandy-Walker Syndrome, 299
DDMP, 344
diazepam
  anesthesia, 150
  anticonvulsant, 80
  in hypoxic ischemic encephalopathy, 361
  stiff horse syndrome, 371
diencephalon, 4, 15
Dimethylsulfoxide, 59, 90
  in hypoxic ischemic encephalopathy, 361
diphenhydramine- in fluphenazine toxicity, 338
diprenorphine, 392
door-banging, 398
dorsal funiculus, 17, 18
dorsal spinocerebellar tract, 17, 18
dourine, 217
Draschia megastoma, 214
dummies, 357
dyskinesia, 365
dysmetria, 71
dysphagia, 109

Eastern equine encephalitis virus, 177
eclampsia, 277
ectoderm, 3
Edinger-Westphal nucleus, 30
electroencephalography, 137
  for hepatic encephalopathy, 263
electromyography, 127
  Australian stringhalt, 347
  equine grass sickness, 246
  equine motor neuron disease, 238
  hyperkalemic period paralysis, 275
  hypomagnesemia, 279
  lead intoxication, 342
  sweeny, 331
emperipolesis, 264
enrofloxacin, 57
equine degenerative myeloencephalopathy, 235
equine grass sickness, 246
  dysphagia, 113
equine herpesvirus, 181
Equine Infectious Anemia virus, 183
equine motor neuron disease, 238
equine protozoal myeloencephalitis, 197
equine reflex hypertonia, 366
extrapyramidal system, 23

fasciculus cuneatus, 12
fasciculus gracilis, 12
fibrillation potentials, 134
fibrotic myopathy, 371
flumazenil, 264
Froins syndrome, 42
fumonisin, 348
furosemide- for increased intracranial pressure, 319

Gamstorps disease, 274
ganglion, 8
geniculate bodies, 15
glossopharyngeal nerve, 11, 110
glutamate, 358

Goldman-Witmer coefficient (see C-value)
golgi tendon organ, 365
Gomen disease, 250
guaifenesin, 343
guttural pouch
  dysphagia, 112
  mycosis/encephalitis, 232

Halicepholobus gingivalis, 213
hay-dipping, 398
head tilt, 101
head trauma, 106
Hendra virus, 183
hepatic encephalopathy, 257
Horner's syndrome, 116
hydrocephalus, 299
hyperkalemia, 273
hyperkalemic periodic paralysis, 274
hyperkinesia, 365
hypermagnesemia, 279
hypermetria, 71
hypernatremia, 271
hypertonic saline
  for traumatic brain injury, 318, 320
  in anesthesia, 152
  for CNS edema, 59
hypocalcemia, 134, 276
Hypoderma spp., 214
hypoglycorrhachia, 42
hypokalemia, 272
hypokinesia, 365
hypometria, 71
hyponatremia, 269
hypothalamus, 15
hypothermia- for traumatic brain injury, 319
hypoxic ischemic encephalopathy, 357

IgG index, 49, 204
imipramine, 392
interferon gamma, 52
intracranial pressure, 37
  anesthesia, 149
  traumatic brain injury, 107

Jamestown Canyon Virus, 181
Japanese encephalitis, 180

Kumri, 218
kyphosis, 300

La Crosse Virus, 181
Lactation tetany (see eclampsia)
lactulose, 265
laryngeal adductory test, 68, 285
lavender foal syndrome, 360
leukoencephalomalacia, 348
lightning strike, 109, 111
Lissauer's tract, 17
locoism, 350
long association fibers, 6
lordosis, 300
Louping Ill virus, 184

magnesium, 278
Main Drain Virus, 181
mal seco, 246
mammillary body, 15
mannitol, 59
  in anesthesia, 152
  in head trauma, 108
  in hypoxic ischemic encephalopathy, 362
  in traumatic brain injury, 319
megaesophagus, 113
Melao virus, 181
Meningitis
  amebic, 232
  bacterial, 187
  cryptococcal, 231
  mycotic, 232
mephenesin, 367
mesencephalon, 4
Methocarbamol (for strychnine toxicity), 343
microglia, 48
Midazolam, 80
  anticonvulsant, 80
  in anesthesia, 150
midbrain (see mesencephalon)
milk sickness, 343
miniasterixis, 258
moldy corn disease (see leukoencephalomalacia)
Monro-Kellie doctrine, 308
morphine, 151
motor unit action potentials, 131
myelin protein P2, 335
myelinopathy, 166
myelomalacia- postanesthesia, 153
myotatic reflex arc, 365
myotonic potentials, 134

nalmefene, 392
naloxone, 321, 392
naltrexone, 392
narcolepsy, 91
Neospora caninum, 197
Neospora hughesi, 197
neural tube, 3, 4
neuroaxonal dystrophy of Morgan horses, 235
neuroborreliosis, 233
neurologic examination, 65
neuromuscular spindle, 365
neuropathy, 166
neuropraxia, 329
neurotmesis, 329
nicotine, 341
Nigerian equine encephalitis virus, 184
nigropallidal encephalomalacia, 344
Nipah virus, 183
nociception, 20
non-steroidal antiinflammatory drugs, 58, 322
nucleus ambiguus, 111
nyctalopia, 115

oligodendrocytes, 48
oral vitamin E tolerance test, 236

pacing, 379
Paralephastrongylus tenuis, 215
paresis, 70
paspalitrem, 350
paspalum staggers, 349
pawing, 379
penicillin, 55
pentobarbitol, 88
peripheral nerves- general anatomy, 28, 29
peripheral neuropathy
  axillary, 332
  brachial plexus, 331, 332
  facial, 330
  femoral, 332
  gluteal, 333
  median, 331, 332
  musculocutaneous, 331, 332
  obturator, 333
  peroneal, 333
  radial, 331, 332
  sciatic, 333
  suprascapular, 331
  ulnar, 331, 332
peripheral neuropathy- post anesthesia, 153
perivascular cuffing, 166
phase reversal, 139
phenobarbital
  anticonvulsant, 84
  in fluphenazine toxicity, 338
  in hypoxic ischemic encephalopathy, 361
phenoxybenzamine (for urinary incontinence), 123
phenytoin
  anticonvulsant, 88
  for stringhalt, 347–348, 367
phenylephrine test (for equine grass sickness), 249
pica, 397
plumbism, 341
polyneuritis equi, 111, 334
positive sharp waves, 134
post-mortem examination, 160
potassium, 272
Powassan Virus, 180
praladoxime chloride, 340
prazosin, 123
primidone, 88
propofol, 151
proprioception, 18, 71
prosencephalon, 4
pulmonary edema, 312

Queckenstedt test, 38

Rabies virus, 172
red nucleus, 23
reflex
  biceps, 72
  cervicoauricular, 69
  cervicofacial, 69
  clasp knife, 71
  dolls eye, 68
  local cervical, 69
  micturition, 121
  patellar, 72
  triceps, 72
  withdrawal, 72
repin, 345
rhinitis sicca, 248
rhombencephalon, 4
Rombergs tes't, 103

rubrospinal tract, 23
Ryegrass staggers, 350

salivatory nucleus, 30
Santa Rosa Virus, 181
Sarcocystis neurona, 197
Scandinavian knuckling horse syndrome, 368
Schiff-Sherrington syndrome, 316
scoliosis, 300
seizures, 77
  treatment, 79
self-mutilation, 379
Setaria labiatopapillosa, 218
shivers, 369
short association fibers, 6
slap test (see laryngeal adductory test)
Snow-shoe hare virus, 181
sodium, 269
sorghum cystitis, 351
spasticity, 71
spina bifida, 4
spinothalamic tract, 17, 20
status epilepticus, 89
stereotypical behavior, 373
stereotypical behavior (treatment), 388
stiff-horse syndrome, 370
strabismus, 114
stringhalt (see equine reflex hypertonia)
Strongylus vulgaris, 213
substantia nigra, 23
Surra, 217
swainsonine, 350
sweeny, 331
synchronous diaphragmatic flutter, 276–277

Tacaiuma virus, 181
telencephalon, 4
tentorial herniation, 107
tetanus, 221
thalamus, 15
theophylline, 361
thiopental, 151
tick paralysis, 113
toxicity
  4-aminopyridine, 343
  Acroptilon repens, 344
  Asclepias subverticullata (western whorled milkweed), 352
  Astragalus spp., 350
  bromide, 340
  bracken fern, 346
  carbamates, 341
  Centaurea solstitialis, 344
  Centaurea melitensis, 344
  Claviceps paspali, 349
  Conium maculata (poison hemlock), 352
  Cicuta maculata (water hemlock), 352
  Duboisia hopwoodii, 341
  Eupatorium rugosum (white snakeroot)
  fluphenazine, 337
  Fusarium spp., 348
  Gomphrena celosioides, 353
  haloxon, 339
  Hypochorius radicata, 367
  horse tail, 347
  ionophore, 339
  ivermectin, 339
  Laburnum anagyroides, 351
  Lathyrus nissolia (grass vetchling), 351
  lead, 341
  levamasol, 339
  lolitrem, 350
  Malta star thistle, 344
  Malva parviflora, 367
  mercury, 341
  metaldehyde, 343
  methiocarb, 343
  moxidectin, 338
  organophosphate, 340
  Oxytropis spp., 350
  poison hemlock, 352
  pipothiazine, 338
  propylene glycol, 339
  Pteridium aquilinum, 345
  Rayless goldenrod, 343
  Russian knapweed, 344
  Robinia pseudoacacia (black locust), 351
  scouring rush (*Equisetum arvense*), 347
  Solanum spp., 344
  Sorghum spp., 351
  strychnine, 343
  Taraxacum officinal, 367
  Trachyandra divaricata (branched onion weed), 353

urea, 340
Urtica dioica (stinging nettles), 353
white snakeroot, 343
yellow star thistle, 344
transverse cerebral fissure, 16
transforming growth factor, 52
traumatic brain injury, 305
trembles, 343
trimethoprim-sulfamethoxazole, 56
Trypanosoma equiperdum, 217
Trypanosoma evansi, 217
tryptophan, 388

upper motor neuron system, 20
urethral pressure profiling, 123
urinary incontinence, 121

vasogenic edema, 309
Venezuelan equine encephalitis virus, 177
ventral funiculus, 17
ventral spinocerebellar tract, 17, 18
verminous myeloencephalitis, 214
vitamin A deficiency, 115

Wallerian degeneration, 166
wanderers, 357
weaving, 378
West Nile virus, 178
Western equine encephalitis virus, 177
wind-sucking, 377
Wobblers syndrome, 283
wood-chewing, 395